Optimal Decision Making in Operations Research and Statistics

Methodologies and Applications

Editors
Irfan Ali, Leopoldo Eduardo Cárdenas-Barrón, Aquil Ahmed and **Ali Akbar Shaikh**

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Preface

Operations Research (OR) has become a powerful technique for optimal decision-making. New techniques and sophisticated analysis tools are required to resolve the challenges arising from modern problems. It leads to the emergence of OR for efficiently determining optimal solutions to problems of real world. Although there are many types of conceivable problems, OR practitioners and researchers have found several problems in different circumstances. Thus, a challenge problem may be in the manufacturing industry area while another may be in the service sector. However, their essential features are the same. Thus, it is possible to describe these problems by naming the general categories into which they fall irrespective of their physical descriptions. A common analytical technique can be used to find the optimal solution to problems belonging to the same general category. In this direction,OR helps make better decision and solve problems in the real world. It uses mathematical relations, statistical computations, engineering techniques, economics and management methodologies to know the consequences of deciding for any possible alternative actions.

The decision-making techniques can be used in industries and services for making business decisions under risk and uncertainty. Furthermore, the decision-making techniques are also applied successfully to almost every possible sphere of human activity. Moreover, decision-making techniques are widely applied in different fields, ranging from almost every branch of science, engineering, industrial management, management planning, medical sciences, social sciences and economics, among others.

The book "Optimal Decision Making in Operations Research & Statistics: Methodologies and Applications" has been written by unified authors with a diverse background expertise from the faculties of Operations Research, Management, Applied Statistics and Mathematics. The contributed chapters are based on the vast research experiences of the authors in real-world decision-making problems.

The book is on the recent developments and contributions in optimal decision-making using optimization and statistical techniques. Mathematical modelling of cost-effective management policies are also part of the book.

The book presents challenging and practical real-world applications based on decision-making problems in various fields. The modelling and solution procedures of such real-world problems are provided concisely. This book provides readers a valuable compendium of several decision-making problems as a reference for this field's researchers and industrial practitioners. After reading this book, the readers will understand the formulations of decision-making problems and their solution procedures using appropriate optimization and statistical techniques.

This book broadly covers applications of applied statistics and optimization techniques in decision making in the various areas such as—estimation, control charts, econometric, regression, sampling, stochastic modelling, inventory control and management, transportation problem and optimization.

Finally, this book benefits the teachers, students, researchers, and industrialists working in material science, especially Operations Research and Applied Statistics, as a valuable reference handbook for teaching, learning, and research.

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Chapter 6

Stochastic Models for Cancer Progression and its Optimal Programming for Control with Chemotherapy

Tirupathi Rao Padi

1. Introduction

Continuous, uninterrupted and unending cell division is usually referred to as carcinogenesis. Formulation of cancer-causing cells in a living body may be due to several reasons. The likely causes are exposure to hazardous environmental conditions, unhealthy food habits, unwarranted life styles, smoking, consumption of toxic beverages, among others. Natural mechanism of cell growth under normal conditions will happen whenever there is a requirement for cell construction due to the wear and tear processes. Normal cells have to undergo processes like cell division, growth, death/differentiation and transformation from one format to the other. Usually a normal/healthy cell will divide into two identical normal/healthy daughter cells, further the two daughter cells divide into subsequent progeny cells. The alleles of genes are used to regulate the mechanism of structured cell division. They play a vital role in protecting the living body from risks like over proliferation of specific cells above the required level and unnecessary invasion of similar cells from the original location to the invasive one. However, when the regulating mechanism disobeys the usual cell division process, the problem of cancer cell growth will come up. The three main factors like genetic materials or proteins or protein-encoding genes are responsible for regulating the cell's division, growth, death/differentiation and invasion to the other tissues. They are namely (i) *proto-oncogene;* responsible for enhancing the cell division, (ii) *tumor suppressor gene;* monitor the cell division or causes the cell death, (iii) *DNA repair gene;* protects the mutation causing gene by means of rectifying its unusual behavior. If mutation occurs in these genes it leads to loss of control of the complete cell cycle and leads to the development of cancer. Moreover, all kinds of cancers are having one of the features that disrupt the process of regulatory mechanism in the normal cell division. The process of abnormal cells growth is initiated with a simple mutation in the regulating genes. The operating characteristics and behavior patterns of cancerous cells are entirely different from those of normal cells. Needless to say that mathematical modelling is a suitable option for studying cancer growth. However, it has numerous limitations as model building is linked with many uncertain conditions. Hence, stochastic modeling is more rational in studying cancer spread and control.

The nature of a malignant tumor is defined with the type of cells in the organ where it is originally initiated. Carcinogenesis is a complex, random and multistep process consisting of initiation, promotion and progression of normal cells (Tan, 1989). Transforming normal cells into malignant cells in any organ is usually initiated with simple mutation in the gene of cells and aggravate with abnormal proliferation. The mutation process involved in normal stage cell to intermediate stage cells and intermediate stage to malignant stage cells are purely random in nature (Quinn, 1997). The cancer cell growth involves a series of molecular changes in the normal cells. While reaching the malignant stage, it may undergo one or more mutation (transformation of one state to another state) processes. The cancer cells have the capability to spread/migrate to neighboring locations of an organ or other part of the body through blood vessels which is termed as the metastasis. The migrated malignant cells form a new colony by means of further proliferation leading to formation of cancer tumors. In the genesis of cancer, the response variables such as cell division, differentiation/death, mutation and migration are subject to random variations. Studying the growth of abnormal cells through stochastic modelling is always a superior approach. Getting the Statistical measures from the observed stochastic possesses through the probability functions shall provide the most relevant picture for proper understanding of cancer cell growth.

There is established literature evidence in making use of deterministic and stochastic study models for carcinogenesis. Normally a cell division shall have to take several mutations to become a malignant cell. Many researchers have developed two/three stage growth stochastic models similar to birth-and-death and mutation processes. Pathophysiological behavior of cancerous cells is modeled with

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suitable assumptions for quantifying functional relations in the contexts of primary and invasive states of growth. There is substantial evidence in mathematical modeling of cancer formation, growth and invasion using the birth and death processes. However, there is a significant lagging in applying the spread of cancer through migration processes. Hence this study is intended to contribute towards the research gap for making use of blended stochastic processes with a backdrop of bivariate and Trivariate birth-death—migration processes. Different states of cancer growth and its dynamics are modeled for exploring the joint probability distributions of the tandem arrival and departure processes. Development of optimization programming problems for regulating the cancer cell's growth with the controlling parameters is still an open problem for study. Optimal drug administration by assessing the varying health indicators through stochastic programming is another focused area where there is no significant evidence on reported research. Predicting the optimal decision parameters from the developed stochastic and optimization models is the core objective of this study. This study can be extended for healthcare management during the treatment of cancer with chemotherapy. Exploring the real time decision support systems from the developed stochastic optimization modeling is the motivating factor for selecting this study.

2. Stochastic Model for Cancer Cell Growth during Chemotherapy

Tirupathi Rao et al., 2011, 2012 have developed a bi-variate stochastic model for normal cell and mutant cell growth during drug administration and drug vacation. These models are for treatment dependent malignant tumor progression based on the assumption that the cell division of pre-malignant and malignant cells follow a Poisson distribution during and off the chemotherapy process. Madhavi et al., 2013 have developed a stochastic model for stage dependent cancer cell growth under the assumption of all possible cell divisions during drug administration and its vacation. Tirupathi Rao et al. (2013) have developed a Trivariate stochastic model for cancer cell growth progression under the assumptions of cell divisions from normal cells to premalignant cells and from premalignant cells to malignant cells during the presence and absence of chemotherapy. The focus of all the above-mentioned works are mostly based on the cancer cell processes within the organ in the region of formation of the cancer cell. They have neither discussed nor developed any prospective cancer growth model as result of migration from the region of formation to the region of destination. Hence, the development of cancer growth through migration of mutant cell or cancer cell deserves the attention of researchers for better understanding of cancer growth behavior/dynamics.

The above said gap of research is taken care of in this chapter. The proposed model will help in knowing the spontaneous and active growth of cells during drug administration and vacation periods. A linear function is defined to express the decision parameters in the dynamics of growth of any organ cell during drug administration and vacation periods using indicator variables. They will define the relationship between the decision parameters of cancer cell growth. This model can study the growth of a cancer cell as an overall phenomenon with drug administration and its vacation. In order to study the characteristics of the model, the first and second order moments were derived. This model will be well suited for carcinogenesis experimental trials. Data can be extracted for the said parameters on sample experimentation basis. However, in order to understand the model behavior and sensitivity analysis a numerical study is carried out with simulated data.

Mutation is a resulting change of cell division behavior due to violation of genetic instructions of cell division. Unusual, continuous and a never-ending cell division process is termed as cancer. This unwarranted cell proliferation within the membrane of a tissue/muscle leads to formation of tumors. However, the connectivity of each cell with the blood circulation system makes the flow of mutant/cancer causing cells to other regions of the body referred to as metastasis. Such cell differentiation, division and death will cause the abnormal structure and functioning of tissues in an organ. It is a threat to the normal and regulating functions of cell growth within the tissue as the initiated mutant cells will be converted to full-fledged accumulated malignant cells. These newly formatted malignant cells will further spread to the other parts of the body from the origin through the process of metastasis. This process will lead to form secondary tumors either in the neighboring places (within the organ where the mutation has occurred) or in distant locations (other location of the body away from the organ where the newly formulated cancer cell was originated). If the cell growth process is deterministic then mathematical models will provide appropriate and accurate results. Whereas for abnormal cell growth processes which are subject to non-deterministic, stochastic models will be suitable alternatives. Here, it is assumed that the behaviour of normal/mutant/malignant cells growth/loss/differentiation are fully stochastic. This process can be modeled with homogeneous birth, death, mutation and migration processes.

Notations & Postulates of the Model

β^*_{ij1} - Growth rate of i^{th} staged cell in j^{th} staged tumor and l^{th} state of drug application

δ^*_{ij1} - Loss rate of i^{th} staged cell in j^{th} staged tumor and l^{th} state of drug application

τ^*_{ij1} - Transformation rate of cell from i^{th} staged cell to $(i+1)^{th}$ staged cell, from the j^{th} staged tumor to $(j+1)^{th}$ staged tumor in l^{th} state of drug application

Where,

i = 1, 2 and 3 are Normal cell, Malignant cell and Migrated Malignant cell respectively

j = 1 and 2 are Primary stage of tumor and Secondary stage of tumor respectively

l = 0 and 1 are drug vacation, drug administration respectively

a_r is an indicator variable representing the drug administration and vacation referred below.

$$a_r = \begin{cases} 1 & ; \text{Drug Ad min istration period} \\ 0 & ; \text{Drug vacation period} \end{cases} \qquad \text{for } r = 1,...,9$$

The growth rate, migration/transformation (mutation) rate and loss rate of cells can be represented as $\beta_{ij}^{*} = \left[a_r\beta_{ijl} + (1-a_r)\beta_{ijl}\right]$; $\tau_{ij}^{*} = \left[a_r\tau_{ijl} + (1-a_r)\tau_{ijl}\right]$; $\delta_{ij}^{*} = \left[a_r\delta_{ijl} + (1-a_r)\delta_{ijl}\right]$ respectively.

The mechanisms involved in the cell divisions, death/ differentiation are purely stochastic during drug administration and vacation periods. Let us assume that the events occurred in non-overlapping intervals of time and are statistically independent in both the periods. The cell's growth, loss and migrations during the drug administration period and drug vacation period are also assumed to be stochastic and a model is developed based on the following postulates.

Let $\{N(t), t \geq 0\}$ be the process of normal cell mechanisms (growth/loss/transformation/migration) and $\{M(t), t \geq 0\}$ be the process of malignant cells mechanism (growth/loss/migration). Let $\{N(t), M(t); t \geq 0\}$ be a joint Bivariate stochastic process of individual stochastic processes of $\{N(t), t \geq 0\}$ and $\{M(t), t \geq 0\}$, the joint probability being $P\{[N(t), M(t)] = [n, m]\} = P_{n,m}(t)$ and, marginal probabilities with respect to the number of normal cells and number of malignant cells are $P\{N(t) = n\} = P_n(t)$ and $P\{M(t) = m\} = P_m(t)$,

Further,

$$P\{N(\Delta t) = u / N(t) = n\} = P_{nu}; \text{ for } u = n+1, n-1, n, n \pm 2$$

$$P\{M(\Delta t) = v / M(t) = m\} = P_{mv}; \text{ for } v = m+1, m-1, m, m \pm 2$$

$$P\left[\{(N(\Delta t), M(\Delta t)) = (u, v)\} / \{(N(t), M(t)) = (n, m)\}\right] = P_{nu,mv}; \text{for } v = m+1, m-1, m, m \pm 2$$

If Δt be a very small interval of time.

Let us now define postulates of the process with respect to normal cells and malignant cells growth,

$$\begin{aligned} p_{n,u} &= P\{N(\Delta t) = u / N(t) = n\} \\ &= n\left(a_1\beta_{111} + (1-a_1)\beta_{110}\right)\Delta t + o(\Delta t) && ; u = n+1 \\ &= n\left(a_5\delta_{111} + (1-a_5)\delta_{110}\right)\Delta t + o(\Delta t) && ; u = n-1 \\ &= n\left(a_2\tau_{111} + (1-a_2)\tau_{111}\right)\Delta t + o(\Delta t) && ; u = n-1 \\ &= 1 - \left[n \begin{pmatrix} (a_1\beta_{111} + (1-a_1)\beta_{110}) \\ + (a_5\delta_{111} + (1-a_5)\delta_{110}) \\ + (a_2\tau_{111} + (1-a_2)\tau_{111}) \end{pmatrix} \Delta t + o(\Delta t) \right] && ; u = n \\ &= o(\Delta t)^2 && ; u = n \pm 2 \end{aligned} \tag{2.1}$$

For malignant cell growth processes,

$$\begin{aligned} p_{m,v} &= P\{M(\Delta t) = v / M(t) = m\} \\ &= m\left(a_3\beta_{211} + (1-a_3)\beta_{210}\right)\Delta t + o(\Delta t) && ; v = m+1 \\ &= m\left(a_6\delta_{211} + (1-a_6)\delta_{210}\right)\Delta t + o(\Delta t) && ; v = m-1 \\ &= m\left(a_7\tau_{211} + (1-a_7)\tau_{210}\right)\Delta t + o(\Delta t) && ; v = m-1 \\ &= \left(a_4\beta_{321} + (1-a_4)\beta_{320}\right)\Delta t + o(\Delta t) && ; v = 1 \\ &= \left(a_8\delta_{321} + (1-a_8)\delta_{320}\right)\Delta t + o(\Delta t) && ; v = 1 \\ &= \left(a_9\tau_{321} + (1-a_9)\tau_{321}\right)\Delta t + o(\Delta t) && ; v = 1 \\ &= 1 - \left[\begin{Bmatrix} m\left[\left(a_3\beta_{211} + (1-a_3)\beta_{210}\right) + \left(a_6\delta_{211} + (1-a_6)\delta_{210}\right)\right] \\ + \left(a_7\tau_{211} + (1-a_7)\tau_{210}\right)\Big] + \Big[\left(a_4\beta_{321} + (1-a_4)\beta_{320}\right) \\ + \left(a_8\delta_{321} + (1-a_8)\delta_{320}\right) + \left(a_9\tau_{321} + (1-a_9)\tau_{321}\right)\Big] \end{Bmatrix} \Delta t + o(\Delta t) \right] && ; v = m \\ &= o(\Delta t)^2 && ; v = m \pm 2 \end{aligned} \tag{2.2}$$

Considering the joint stochastic processes of normal cells and malignant cells dynamics during drug vacation period and drug administration period, we have

$$
\begin{aligned}
p_{nu,mv} &= P\left\{\left(N(\Delta t), M(\Delta t)\right) = (u,v) / \left(N(t), M(t)\right) = (n,m)\right\} \\
&= n\left(a_1\beta_{111} + (1-a_1)\beta_{110}\right)\Delta t + o(\Delta t) && ; u = n+1, v = m \\
&= n\left(a_5\delta_{111} + (1-a_5)\delta_{110}\right)\Delta t + o(\Delta t) && ; u = n-1, v = m \\
&= n\left(a_2\tau_{111} + (1-a_2)\tau_{111}\right)\Delta t + o(\Delta t) && ; u = n-1, v = m \\
&= m\left(a_3\beta_{211} + (1-a_3)\beta_{210}\right)\Delta t + o(\Delta t) && ; u = n, v = m+1 \\
&= m\left(a_6\delta_{211} + (1-a_6)\delta_{210}\right)\Delta t + o(\Delta t) && ; u = n, v = m-1 \\
&= m\left(a_7\tau_{211} + (1-a_7)\tau_{210}\right)\Delta t + o(\Delta t) && ; u = n, v = m-1 \\
&= \left(a_4\beta_{321} + (1-a_4)\beta_{320}\right)\Delta t + o(\Delta t) && ; u = n, v = 1 \\
&= \left(a_8\delta_{321} + (1-a_8)\delta_{320}\right)\Delta t + o(\Delta t) && ; u = n, v = 1 \\
&= \left(a_9\tau_{321} + (1-a_9)\tau_{320}\right)\Delta t + o(\Delta t) && ; u = n, v = 1 \\
&= 1 - \left[\begin{array}{l}
n\left[\left(a_1\beta_{111} + (1-a_1)\beta_{110}\right) + \left(a_5\delta_{111} + (1-a_5)\delta_{110}\right)\right. \\
\left. + \left(a_2\tau_{111} + (1-a_2)\tau_{111}\right)\right] + m\left[\left(a_3\beta_{211} + (1-a_3)\beta_{210}\right)\right. \\
\left. + \left(a_6\delta_{211} + (1-a_6)\delta_{210}\right) + \left(a_7\tau_{211} + (1-a_7)\tau_{210}\right)\right] \\
+ \left[\left(a_4\beta_{321} + (1-a_4)\beta_{320}\right) + \left(a_8\delta_{321} + (1-a_8)\delta_{320}\right)\right. \\
\left. + \left(a_9\tau_{321} + (1-a_9)\tau_{320}\right)\right]
\end{array}\right]\Delta t + o(\Delta t) \\
& && ; u = n, v = m \\
&= o(\Delta t)^2 && ; u = n \pm 2, v = m \pm 2
\end{aligned}
\tag{2.3}
$$

Differential Equations & Probability Generating Functions of the Model:

Let $p_{n,m}(t+\Delta t)$ be the probability that the occurrence of any one possible event such as cell division, differentiation/death, transformation/ migration in an infinitesimal interval Δt, on the condition that there exist 'n' normal cells and 'm' malignant cells in the organ up to time 't' during the period of drug administration and drug vacation period.

$$
\begin{aligned}
p_{n,m}(t+\Delta t) = &\left\{1 - \left\{n\left[\left(a_1\beta_{111} + (1-a_1)\beta_{110}\right) + \left(a_2\tau_{111} + (1-a_2)\tau_{111}\right) + \left(a_5\delta_{111} + (1-a_5)\delta_{110}\right)\right]\right.\right. \\
&+ m\left[\left(a_3\beta_{211} + (1-a_3)\beta_{210}\right) + \left(a_6\delta_{211} + (1-a_6)\delta_{210}\right) + \left(a_7\tau_{211} + (1-a_7)\tau_{210}\right)\right] \\
&\left.\left. + \left[\left(a_4\beta_{321} + (1-a_4)\beta_{320}\right) + \left(a_8\delta_{321} + (1-a_8)\delta_{320}\right) + \left(a_9\tau_{321} + (1-a_9)\tau_{320}\right)\right]\right\}\Delta t\right\} p_{n,m}(t) \\
&+ p_{n+1,m}(t)\left[(n-1)\left(a_1\beta_{111} + (1-a_1)\beta_{110}\right)\right] + p_{n+1,m-1}(t)\left[(n+1)\left(a_2\tau_{111} + (1-a_2)\tau_{111}\right)\right]\Delta t \\
&+ p_{n,m-1}(t)\left[(m-1)\left(a_3\beta_{211} + (1-a_3)\beta_{210}\right)\right] + p_{n+1,m}(t)\left[(n+1)\left(a_5\delta_{111} + (1-a_5)\delta_{110}\right)\right]\Delta t \\
&+ p_{n,m+1}(t)\left[(m+1)\left(a_6\delta_{211} + (1-a_6)\delta_{210}\right)\right] + p_{n,m+1}(t)\left[(m+1)\left(a_7\tau_{211} + (1-a_7)\tau_{210}\right)\right]\Delta t \\
&+ p_{n,m-1}(t)\left(a_4\beta_{321} + (1-a_4)\beta_{320}\right)\Delta t + p_{n,m+1}(t)\left(a_8\delta_{321} + (1-a_8)\delta_{320}\right)\Delta t \\
&+ p_{n,m+1}(t)\left(a_9\tau_{321} + (1-a_9)\tau_{320}\right)\Delta t + o(\Delta t^2) \qquad \text{for } n, m \geq 1
\end{aligned}
\tag{2.4}
$$

The initial conditions are

$$
p_{N_0,M_0}(0) = 1,\ p_{i,j}(0) = 0 \quad \forall i \neq N_0; j \neq M_0 \tag{2.5}
$$

The differential equations of the model when Δt tends to zero with the above equation are

$$\begin{aligned}
p'_{n,m}(t) = &-\{n[(a_1\beta_{111}+(1-a_1)\beta_{110})+(a_2\tau_{111}+(1-a_2)\tau_{111})+(a_5\delta_{111}+(1-a_5)\delta_{110})]\\
&+m[(a_3\beta_{211}+(1-a_3)\beta_{210})+(a_6\delta_{211}+(1-a_6)\delta_{210})+(a_7\tau_{211}+(1-a_7)\tau_{210})]\\
&+[(a_4\beta_{321}+(1-a_4)\beta_{320})+(a_8\delta_{321}+(1-a_8)\delta_{320})+(a_9\tau_{321}+(1-a_9)\tau_{320})]\}p_{n,m}(t)\\
&+p_{n+1,m}(t)[(n-1)(a_1\beta_{111}+(1-a_1)\beta_{110})]+p_{n+1,m-1}(t)[(n+1)(a_2\tau_{111}+(1-a_2)\tau_{111})]\\
&+p_{n,m-1}(t)[(m-1)(a_3\beta_{211}+(1-a_3)\beta_{210})]+p_{n+1,m}(t)[(n+1)(a_5\delta_{111}+(1-a_5)\delta_{110})]\\
&+p_{n,m+1}(t)[(m+1)(a_6\delta_{211}+(1-a_6)\delta_{210})]+p_{n,m+1}(t)[(m+1)(a_7\tau_{211}+(1-a_7)\tau_{210})]\\
&+p_{n,m-1}(t)(a_4\beta_{321}+(1-a_4)\beta_{320})+p_{n,m+1}(t)(a_8\delta_{321}+(1-a_8)\delta_{320})\\
&+p_{n,m+1}(t)(a_9\tau_{321}+(1-a_9)\tau_{320}) \qquad \text{for } n,m\geq 1
\end{aligned} \tag{2.6}$$

$$\begin{aligned}
\frac{dp_{0,1}(t)}{dt} = &-[(a_3\beta_{211}+(1-a_3)\beta_{210})+(a_4\beta_{321}+(1-a_4)\beta_{320})+(a_6\delta_{211}+(1-a_6)\delta_{210})\\
&+(a_8\delta_{321}+(1-a_8)\delta_{320})+(a_9\tau_{321}+(1-a_9)\tau_{320})]P_{0,1}(t)+(a_5\delta_{111}+(1-a_5)\delta_{110})p_{1,1}(t)\\
&+(a_2\tau_{111}+(1-a_2)\tau_{111})p_{1,0}(t)+\{2[(a_6\delta_{211}+(1-a_6)\delta_{210})+(a_7\tau_{211}+(1-a_7)\tau_{210})]\\
&+(a_8\mu_{321}+(1-a_8)\mu_{320})+(a_9\tau_{321}+(1-a_9)\tau_{320})\}p_{0,2}(t)+(a_4\beta_{321}+(1-a_4)\beta_{320})p_{0,0}(t)
\end{aligned} \tag{2.7}$$

$$\begin{aligned}
\frac{dp_{1,0}(t)}{dt} = &-\{(a_1\beta_{111}+(1-a_1)\beta_{110})+(a_2\tau_{111}+(1-a_2)\tau_{111})+(a_4\beta_{321}+(1-a_4)\beta_{320})\\
&+(a_5\delta_{111}+(1-a_5)\delta_{110})+(a_7\tau_{211}+(1-a_7)\tau_{210})+(a_8\delta_{321}+(1-a_8)\delta_{320})\\
&+(a_9\tau_{321}+(1-a_9)\tau_{320})\}p_{1,0}(t)+2(a_5\delta_{111}+(1-a_5)\delta_{110})p_{2,0}(t)\\
&+\{(a_5\delta_{111}+(1-a_5)\delta_{110})+(a_7\tau_{211}+(1-a_7)\tau_{210})+(a_8\delta_{321}+(1-a_8)\delta_{320})\\
&+(a_9\tau_{321}+(1-a_9)\tau_{320})\}p_{1,1}(t)
\end{aligned} \tag{2.8}$$

$$\begin{aligned}
\frac{dp_{0,0}(t)}{dt} = &-\{(a_4\beta_{321}+(1-a_4)\beta_{320})+(a_8\delta_{321}+(1-a_8)\delta_{320})+(a_9\tau_{321}+(1-a_9)\tau_{320})\}p_{0,0}(t)\\
&+(a_5\delta_{111}+(1-a_5)\delta_{110})p_{1,0}(t)+\{(a_5\delta_{111}+(1-a_5)\delta_{110})+(a_7\tau_{211}+(1-a_7)\tau_{210})\\
&+(a_8\delta_{321}+(1-a_8)\delta_{320})+(a_9\tau_{321}+(1-a_9)\tau_{320})\}p_{0,1}(t)
\end{aligned} \tag{2.9}$$

Let P(x, y; t) be the probability generating function of random variable X(t) and Y(t) representing the number of normal cells and number of malignant cells in an organ during the drug administration and vacation period with probability function $P_{n,m}(t)$. Where, $P(x,y;t)=\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}x^n y^m p_{n,m}(t))\ ;|x|<1,|y|<1$.

Multiplying the above differential Equations from (2.6) to (2.9) with $x^n y^m$ and summing over n, m, we get

$$\begin{aligned}
\frac{dP(x,y;t)}{dt} = &-[(a_1\beta_{111}+(1-a_1)\beta_{110})+(a_2\tau_{111}+(1-a_2)\tau_{111})+(a_5\delta_{111}+(1-a_5)\delta_{110})]x\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}nx^{n-1}y^m p_{n,m}(t)\\
&-[(a_3\beta_{211}+(1-a_3)\beta_{210})+(a_6\delta_{211}+(1-a_6)\delta_{210})+(a_7\tau_{211}+(1-a_7)\tau_{210})]y\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}mx^n y^{m-1}p_{n,m}(t)\\
&-[(a_4\beta_{321}+(1-a_4)\beta_{320})+(a_8\delta_{321}+(1-a_8)\delta_{320})+(a_9\tau_{321}+(1-a_9)\tau_{320})]\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}x^n y^m p_{n,m}(t)\\
&+(a_1\beta_{111}+(1-a_1)\beta_{110})x^2\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(n-1)x^{n-2}y^m p_{n+1,m}(t)\\
&+(a_2\tau_{111}+(1-a_2)\tau_{111})y\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(n+1)x^n y^{m-1}p_{n+1,m-1}(t)\\
&+(a_3\beta_{211}+(1-a_3)\beta_{210})y^2\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(m-1)x^n y^{m-2}p_{n,m-1}(t)
\end{aligned}$$

$$
\begin{aligned}
&+\left(a_5\delta_{111}+(1-a_5)\delta_{110}\right)\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(n+1)x^n y^m p_{n+1,m}(t)\\
&+\left[\left(a_6\delta_{211}+(1-a_6)\delta_{210}\right)+\left(a_7\tau_{211}+(1-a_7)\tau_{210}\right)\right]\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(m+1)x^n y^m p_{n,m+1}(t)\\
&+\left[\left(a_8\delta_{321}+(1-a_8)\delta_{320}\right)+\left(a_9\tau_{321}+(1-a_9)\tau_{320}\right)\right]\frac{1}{y}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}x^n y^{m+1}p_{n,m+1}(t)\\
&+\left(a_4\beta_{321}+(1-a_4)\beta_{320}\right)y\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}x^n y^{m-1}p_{n,m-1}(t)
\end{aligned}
\tag{2.10}
$$

where

$$
\frac{dP(x,y;t)}{dx}=\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}nx^{n-1}y^m p_{n,m}(t)=\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(n-1)x^{n-2}y^m p_{n-1,m}(t)
$$

$$
\frac{dP(x,y;t)}{dy}=\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}mx^{n-1}y^m p_{n,m}(t)=\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}(m-1)x^{n-1}y^{m-2}p_{n,m-1}(t)
$$

On simplification, we obtain the differential equation of the form given below,

$$
\begin{aligned}
\frac{\partial}{\partial t}P(x,y;t)=&\left\{-\left[\left(a_1\beta_{111}+(1-a_1)\beta_{110}\right)+\left(a_2\tau_{111}+(1-a_2)\tau_{111}\right)+\left(a_5\delta_{111}+(1-a_5)\delta_{110}\right)\right]x\right.\\
&\left.+\left(a_5\delta_{111}+(1-a_5)\delta_{110}\right)+\left(a_1\beta_{111}+(1-a_1)\beta_{110}\right)x^2+\left(a_2\tau_{111}+(1-a_2)\tau_{111}\right)y\right\}\frac{\partial P(x,y;t)}{\partial x}\\
&+\left\{-\left[\left(a_3\beta_{211}+(1-a_3)\beta_{210}\right)+\left(a_6\delta_{211}+(1-a_6)\delta_{210}\right)+\left(a_7\tau_{211}+(1-a_7)\tau_{210}\right)\right]y\right.\\
&\left.+\left(a_3\beta_{211}+(1-a_3)\beta_{210}\right)y^2+\left(a_6\delta_{211}+(1-a_6)\delta_{210}\right)+\left(a_7\tau_{211}+(1-a_7)\tau_{210}\right)\right\}\frac{\partial P(x,y;t)}{\partial y}\\
&+\left\{-\left[\left(a_4\beta_{321}+(1-a_4)\beta_{320}\right)+\left(a_8\delta_{321}+(1-a_8)\delta_{320}\right)+\left(a_9\tau_{321}+(1-a_9)\tau_{320}\right)\right]\right.\\
&\left.+\left[\left(a_8\delta_{321}+(1-a_8)\delta_{320}\right)+\left(a_9\tau_{321}+(1-a_9)\tau_{320}\right)\right]y^{-1}+\left(a_4\beta_{321}+(1-a_4)\beta_{320}\right)y\right\}P(x,y;t)
\end{aligned}
\tag{2.11}
$$

We can obtain the characteristics of the model by using joint cumulant generating function of $p_{n,m}(t)$. Let $K(u, v\ t) = \log P(e^u, e^v, t)$ denote the cumulant generating function. By taking the Jacobian transformation of $x = e^u$ AND $y = e^v$ in the probability generating function, the joint cumulant generating function K(u, v, t) of the PGF P(x, y, t) is as the following expression

$$
\begin{aligned}
&\frac{\partial}{\partial t}K(u,v;t)\\
&=\left\{-\left[\left(a_1\beta_{111}+(1-a_1)\beta_{110}\right)+\left(a_2\tau_{111}+(1-a_2)\tau_{111}\right)+\left(a_5\delta_{111}+(1-a_5)\delta_{110}\right)\right]\right.\\
&\quad\left.+\left(a_5\delta_{111}+(1-a_5)\delta_{110}\right)e^{-u}+\left(a_1\beta_{111}+(1-a_1)\beta_{110}\right)e^{u}+\left(a_2\tau_{111}+(1-a_2)\tau_{111}\right)e^{v-u}\right\}\frac{\partial K(u,v;t)}{\partial u}\\
&\quad+\left\{-\left[\left(a_3\beta_{211}+(1-a_3)\beta_{210}\right)+\left(a_6\delta_{211}+(1-a_6)\delta_{210}\right)+\left(a_7\tau_{211}+(1-a_7)\tau_{210}\right)\right]\right.\\
&\quad\left.+\left(a_3\beta_{211}+(1-a_3)\beta_{210}\right)e^{v}+\left[\left(a_6\delta_{211}+(1-a_6)\delta_{210}\right)+\left(a_7\tau_{211}+(1-a_7)\tau_{210}\right)\right]e^{-v}\right\}\frac{\partial K(u,v;t)}{\partial v}\\
&\quad+\left\{-\left[\left(a_4\beta_{321}+(1-a_4)\beta_{320}\right)+\left(a_8\delta_{321}+(1-a_8)\delta_{320}\right)+\left(a_9\tau_{321}+(1-a_9)\tau_{320}\right)\right]\right.\\
&\quad\left.+\left[\left(a_8\delta_{321}+(1-a_8)\delta_{320}\right)+\left(a_9\tau_{321}+(1-a_9)\tau_{320}\right)\right]e^{-v}+\left(a_4\beta_{321}+(1-a_4)\beta_{320}\right)e^{v}\right\}K(u,v;t)
\end{aligned}
\tag{2.12}
$$

3. Statistical Measures & Moments

By making use of the cumulant generating function (CGF),

$$
K(u,v;t)=u\,m^*_{1,0}(t)+v\,m^*_{0,1}(t)+\frac{1}{2}u^2\,m^*_{2,0}(t)+\frac{1}{2}v^2\,m^*_{0,2}(t)+uv\,m^*_{1,1}(t)+\cdots \tag{3.1}
$$

Where $m_{i,j}(t)$ denotes the moments of order (i, j) of the normal cells, malignant cells in an organ at time t under the drug vacation period and drug administration period.

$m^*_{1,0}(t)$ = E[x(t)] - Expected number of normal cells in an organ at time't'

$m^*_{1,0}(t)$ = E[y(t)] - Expected number of malignant cells in an organ at time't'

$m^*_{2,0}(t)$ = Var[x(t)] - Variance of number of normal cells in an organ at time't'

$m^*_{2,0}(t)$ = Var[y(t)] - Variance of malignant cells in an organ at time't'.

$m^*_{1,1}(t)$ = Cov[x(t)y(t)] - Covariance between the number of normal cells and number of malignant cells in an organ at time't'.

On expanding the Equation (2.9) and applying the regulating conditions of cumulant generating function, the following linear differential equations are obtained.

$$\frac{d\,m^*_{1,0}(t)}{dt} = \left(\beta^*_{11} - \tau^*_{11} - \delta^*_{11}\right) m^*_{1,0}(t) \tag{3.2}$$

$$\frac{d\,m^*_{0,1}(t)}{dt} = \tau^*_{11} m^*_{1,0}(t) + \left(\beta^*_{21} - \delta^*_{21} - \tau^*_{21}\right) m^*_{0,1}(t) \tag{3.3}$$

$$\frac{d\,m^*_{2,0}(t)}{dt} = 2\left(\beta^*_{11} - \tau^*_{11} - \delta^*_{11}\right) m^*_{2,0}(t) + \left(\beta^*_{11} + \tau^*_{11} + \delta^*_{11}\right) m^*_{1,0}(t) \tag{3.4}$$

$$\begin{aligned}\frac{d\,m^*_{0,2}(t)}{dt} &= \tau^*_{11} m^*_{1,0}(t) + \left(\beta^*_{21} + \delta^*_{21} + \tau^*_{21}\right) m^*_{0,1}(t) + 2\left(\beta^*_{21} - \delta^*_{21} - \tau^*_{21}\right) m^*_{0,2}(t) \\ &\quad + 2\left(\beta^*_{32} - \delta^*_{32} - \tau^*_{32}\right) m^*_{0,1}(t) + \tau^*_{11} m^*_{1,1}(t)\end{aligned} \tag{3.5}$$

$$\begin{aligned}\frac{d\,m^*_{1,1}(t)}{dt} &= \left(\beta^*_{11} - \tau^*_{11} - \delta^*_{11}\right) m^*_{1,1}(t) + 2\tau^*_{11} m^*_{2,0}(t) - \tau^*_{11} m^*_{1,0}(t) + \left(\beta^*_{21} - \delta^*_{21} - \tau^*_{21}\right) m^*_{1,1}(t) \\ &\quad + \left(\beta^*_{32} - \delta^*_{32} - \tau^*_{32}\right) m^*_{1,0}(t)\end{aligned} \tag{3.6}$$

From (3.2) $\frac{d\,m^*_{1,0}(t)}{dt} = \left(\beta^*_{11} - \tau^*_{11} - \delta^*_{11}\right) m^*_{1,0}(t)$ with $m_{1,0}(0) = N_0$

On solving the above with the given initial condition, $m^*_{1,0}(t) = E[y(t)] = N_0 e^{A^* t}$ (3.7)

From (3.3) $\frac{d\,m^*_{0,1}(t)}{dt} = \tau^*_{11} m^*_{1,0}(t) + \left(\beta^*_{21} - \delta^*_{21} - \tau^*_{21}\right) m^*_{0,1}(t)$ with $m^*_{1,0}(0) = M_0$; Substituting $m_{0,1}(t)$ in the above equation and solving under the given initial condition,

$$m^*_{0,1}(t) = \frac{\tau^*_{11} N_0 e^{A^* t}}{A^* - B^*} + \left(M_0 - \frac{\tau^*_{11} N_0}{A^* - B^*}\right) e^{B^* t} \tag{3.8}$$

From (3.4) $\frac{d\,m^*_{2,0}(t)}{dt} = 2\left(\beta^*_{11} - \tau^*_{11} - \delta^*_{11}\right) m^*_{2,0}(t) + \left(\beta^*_{11} + \tau^*_{11} + \delta^*_{11}\right) m^*_{1,0}(t)$ with $m^*_{2,0}(0) = 0$. Substituting $m^*_{2,0}(t)$ and solving the above equation based on given initial condition,

$$m^*_{2,0}(t) = \frac{D^* N_0 e^{A^* t}}{A^*}\left(e^{A^* t} - 1\right) \tag{3.9}$$

From (3.5) $\frac{d\,m^*_{0,2}(t)}{dt} = \tau^*_{11} m^*_{1,0}(t) + \left(\beta^*_{21} + \delta^*_{21} + \tau^*_{21}\right) m^*_{0,1}(t) + 2\left(\beta^*_{21} - \delta^*_{21} - \tau^*_{21}\right) m^*_{0,2}(t)$ with

$+ 2\left(\beta^*_{32} - \delta^*_{32} - \tau^*_{32}\right) m^*_{0,1}(t) + \tau^*_{11} m^*_{1,1}(t)$

$m^*_{2,0}(0) = 0$. Substituting $m^*_{1,0}(t)$, $m^*_{0,1}(t)$, and solving the above equation with the given initial condition,

$$
\begin{aligned}
m^*_{0,2}(t) &= \frac{\tau^*_{11}N_0e^{A^*t}}{(A^*-2B^*)} + (F^*+2E^*)\left\{\frac{\tau^*_{11}N_0e^{A^*t}}{(A^*-2B^*)(A-B^*)} - \left(M_0 - \frac{\tau^*_{11}N_0}{(A^*-B^*)}\right)\frac{e^{B^*t}}{B^*}\right\} \\
&+ \tau^*_{11}\left\{\begin{array}{l}\dfrac{\tau^*_{11}N_0D^*}{A^*}\left(\dfrac{e^{2A^*t}}{2(A^*-B^*)^2} + \dfrac{e^{A^*t}}{(A^*-2B^*)B^*}\right) - \dfrac{(E^*-\tau^*_{11})N_0e^{A^*t}}{(A^*-2B^*)B^*} \\ -\left(\dfrac{\tau^*_{11}N_0D^* - (A^*-B^*)(E^*-\tau^*_{11})N_0}{(A^*-B^*)B^*}\right)\dfrac{e^{(A^*+B^*)t}}{(A^*-B^*)}\end{array}\right\} \\
&- \left\{\begin{array}{l}\dfrac{\tau^*_{11}N_0}{(A^*-2B^*)} + (F^*+2E^*)\left(\dfrac{\tau^*_{11}N_0 - (A^*-2B^*)M_0}{2(A^*-2B^*)(A^*-B^*)^2B^*}\right) \\ +\tau^{*2}_{11}N_0\left(\dfrac{2(A^*-B^*)(\tau^*_{11}-E^*) + D^*\tau^*_{11}}{2(A^*-2B^*)(A^*-B^*)^2}\right)\end{array}\right\}e^{2B^*t}
\end{aligned}
\tag{3.10}
$$

From (3.6) $\dfrac{dm^*_{1,1}(t)}{dt} = (\beta^*_{11}-\tau^*_{11}-\delta^*_{11})m^*_{1,1}(t) + 2\tau^*_{11}m^*_{2,0}(t) - \tau^*_{11}m^*_{1,0}(t) + (\beta^*_{21}-\delta^*_{21}-\tau^*_{21})m^*_{1,1}(t)$

$$+ (\beta^*_{32}-\delta^*_{32}-\tau^*_{32})m^*_{1,0}(t)$$

with $m^*_{1,1}(0) = 0$. Substituting $m^*_{1,0}(t)$ and $m^*_{2,0}(t)$; solving the above equation using the given initial condition,

$$
\begin{aligned}
m^*_{1,1}(t) &= \left\{\frac{(E^*-\tau^*_{11})N_0e^{-B^*t}}{-B^*} + \frac{\tau^*_{11}D^*N_0}{A^*}\left(\frac{e^{2A^*t}}{(A^*-B^*)} + \frac{e^{A^*t}}{B^*}\right)\right\} \\
&+ \left\{\frac{\tau^*_{11}D^*N_0 - (A^*-B^*)(E^*-\tau^*_{11})N_0}{(A^*-B^*)B^*}\right\}e^{(A^*+B^*)t}
\end{aligned}
$$

Where, N_0 & M_0 – are the initial number of normal and mutant cells in an organ

$$
\begin{array}{lll}
A^* = \beta^*_{11} - \tau^*_{11} - \delta^*_{11} & B^* = \beta^*_{21} - \delta^*_{21} - \tau^*_{21} & D^* = \beta^*_{11} + \tau^*_{11} + \delta^*_{11} \\
E^* = \beta^*_{32} - \delta^*_{32} - \tau^*_{32} & F^* = \beta^*_{21} + \delta^*_{21} + \tau^*_{21} & - \\
\beta^*_{11} = a_1\beta_{111} + (1-a_1)\beta_{110} & \tau^*_{11} = a_2\tau_{111} + (1-a_2)\tau_{110} & \beta^*_{21} = a_3\beta_{211} + (1-a_3)\beta_{210} \\
\beta^*_{32} = a_4\beta_{321} + (1-a_4)\beta_{320} & \delta^*_{11} = a_5\delta_{111} + (1-a_5)\delta_{110} & \delta^*_{21} = a_6\delta_{211} + (1-a_6)\delta_{210} \\
\tau^*_{21} = a_7\tau_{211} + (1-a_7)\tau_{210} & \delta^*_{32} = a_8\delta_{321} + (1-a_8)\delta_{320} & \tau^*_{32} = a_9\tau_{321} + (1-a_9)\tau_{320}
\end{array}
\tag{3.11}
$$

Hence, the characteristics of the model representing the period of drug administration and period of drug vacations are obtained as

- Average number of normal cells in an organ at time‘t’ is $m_{1,0}(t)$;
- Average number of malignant cells in an organ at time‘t’ is $m_{0,1}(t)$;
- Variance of number of normal cells in the organ $m_{2,0}(t)$;
- Variance of number of mutant cells in the organ at time‘t’ is $m^*_{0,2}(t)$;
- Covariance of number of normal and mutant cells in an organ at time ‘t’ is $m^*_{1,1}(t)$.

4. Sensitivity Analysis

In order carry out a better understanding of the developed models, a numerical illustration is considered. The variations in different moments on the number of cells in an organ during the periods of drug administration and vacation are observed by changing value of one parameter keeping the other parameters constant. The computed values of the characteristics of the model $m^*_{1,0}(t)$ $m^*_{0,1}(t)$ $m^*_{2,0}(t)$ $m^*_{0,2}(t)$ and $m^*_{1,1}(t)$ mentioned above from Equations (3.7) to (3.11) for the parameters are presented in the tables using the stimulated

data sets for changing values of β_{111}, β_{110}, τ_{111}, τ_{110}, β_{211}, β_{210}, β_{321}, β_{320}, δ_{111}, δ_{110}, δ_{211}, δ_{210}, τ_{211}, τ_{210}, δ_{321}, δ_{320}, τ_{321}, τ_{320} N_0, M_0, t. The linear function defined using an indicator function a_r has taken values 0 and 1.

Sensitivity Analysis during drug vacation period

This deals with the assumption of $a_r = 0$, r =1,..,9. It has focused on the study of explaining the variation in different statistical measures of cell counts in an organ during the complete absence of a drug in the cancer affected body. The respective tables will give the variation in the statistical measures with respect to the changes in a single decision parameter when all other parameters are constant. Appendix IV (a) deals with fixed parameter values of $\beta_{110} = 1.0$, $\tau_{110} = 0.1$, $\beta_{210} = 4$, $\beta_{320} = 0.3$, $\delta_{110} = 0.5$, $\delta_{210} = 0.5$, $\tau_{210} = 0.3$, $\delta_{320} = 0.03$, $\tau_{320} = 0.01$, $N_0 = 200$, $M_0 = 500$, t = 2 and changing values of one among given parameters.

From the Appendix IV (a), it is observed that average and variance of number of normal cells is an increasing function of β_{110}, average number of malignant cells is an increasing function of β_{110}, variance of number of malignant cells is a decreasing function of β_{110}. The average & variance of numbers of normal cells are decreasing functions of τ_{110}; average and variance of number of malignant cells are increasing and decreasing functions of τ_{110} respectively. The average and variance of numbers of malignant cells are increasing functions of β_{210}. The variance of number of malignant cells is an increasing function of β_{320}. The average number of normal & malignant cells and variance of number of normal cells are decreasing functions of δ_{110}; variance of number of malignant cells is an increasing function of δ_{110}. The average & variance of number of malignant cells covariance between the normal and malignant cells are a decreasing function of δ_{210}. The average & variance numbers of malignant cells and covariance between cells are a decreasing function of τ_{210}. The variance of number of malignant cells and covariance between normal and malignant cells are decreasing functions of δ_{320}. The variance of number of malignant cells and covariance between normal and malignant cells are decreasing function of τ_{320}. The average & variance of number of normal & malignant cells along are increasing functions of time.

Sensitivity Analysis during drug administration period

This deals with the assumption of a_r=1, r=1,..,9. It has focused on the study of explaining the variation in different statistical measures of cell counts in an organ during complete presence of a drug in the cancer affected body. The respective tables will give the variation in statistical measures with respect to the changes in a single decision parameter when all other parameters are constant. Appendix IV (b) deals with changing values of one parameter and fixed value of remaining parameters of the set of parameters under study.

From the Appendix IV (b), it is observed that the average and variance of number of normal and malignant cells are increasing functions of β_{111}. The average number of normal cells and variance of number of malignant cells are decreasing functions of τ_{111}; average number of malignant cells and variance of number of normal cells are increasing functions of τ_{111}. The average & variance of number of malignant cells are increasing functions of β_{211}. The variance of number of malignant cells is an increasing function of β_{321}. The average and variance of number of normal and malignant cells is a decreasing function of δ_{111}. The average and variance of number of malignant cells are decreasing functions of δ_{211}. The average and variance of number of malignant cells are decreasing functions of τ_{211}. The variance of number of malignant cells is a decreasing function of δ_{321}. The variance of number of malignant cells is a decreasing function of τ_{321}. The average and variance of number of normal and malignant cells are an increasing function of N_0. The average and variance of number of malignant cells are an increasing function of M_0. The average number of normal & malignant cells and variance of number of normal & malignant cells are an increasing function of time.

Summary and Results

It is with regard to constructing the stochastic model and sensitivity analysis, a bivariate stochastic model is developed for the cancer cell growth in an organ based on homogeneous birth, death, mutation and migration processes under the period of drug administration and vacation by defining a linear function with an indicator variable. The differential difference equations are derived with the help of postulates possessing the model. The classical probability generating function approach is applied to represent the model in terms of partial differential equations for the random variables X(t) and Y(t) for the number of normal cells and number of malignant cells respectively during the drug administration period and drug vacation period. The first and second order moments are derived through cumulant generating functions. The numerical study was carried out to study the model behaviour for varying parameters during the period of drug administration and vacation. This study will help the medical practitioner to understand the behaviour of the cancer and dynamics in the cell growth over a period of time. Proper understanding about behaviour of cancer cell growth will give inputs to the medical practitioner regarding the condition of the patient. Treatment protocols can be designed with the developed model. Further, the statistical moments in this chapter were used for constructing the optimization programming problems in the following section.

5. Optimization Model for Cancer Control

The core objective of this section is to explore the optimal decision parameters which play a vital role in the processes of growth, death and invasion rates of cancer cells during drug vacation (absences of drug) and administration periods (presence of drug).

It is observed from the literature that several attempts have been made to predict the decision parameters in the abnormal cell dynamics (Tirupathi Rao, 2012). This study proposed the decision-making optimization models for minimizing the average number of malignant cells (or cancer cells), maximizing the average number of normal cells (or healthy cells), minimizing the variability (volatility) in the growth of normal cells, maximizing the variability in the growth of malignant (or cancer) cells, among other things. All the proposed programming problems shall have the common constraints such as average number of normal cells should be within threshold limits, average number of malignant cells should be lower than a specific danger limit, variance of the number of normal cells should be in a narrower range and variance of number of malignant cells should be in a wider range, are taken into account for the problem (Tirupathi Rao, 2012, 2013, 2014).

Optimal Programming for Cancer Control & Progression during Drug Administration

All the above-cited studies have considered the programming problems as a simple variable presentation and have solved each separately. They have considered the variables like average number normal and malignant cells, variance of normal and malignant cells, among others. However, in this study the researcher has addressed programming problems with a variable ratio between the normal and malignant cell growth. This approach will provide the relative behavior of the study variables. They can provide the comparative movements between the observed variables. While studying the growth or loss dynamics of cancer cells, desired situations like (i) the average number of healthy cells should always be greater than the average number of mutant or malignant cells and (ii) The variance of normal/healthy cells should always be less than the variance of mutant/malignant cells have to be taken in to consideration for better understanding. The phenomenon of programming problem formulation of programming has been carried out with two notions namely (i) in general context (assuming patient is not in treatment) and (ii) in drug administration context (the patient is in treatment). The objective functions are formulated with the relative measures (ratio between normal and mutant cells). First objective is to Minimize, where is the ratio between average number of normal cells to the average number of malignant cells and the second objective is to minimize the, where is the ratio between variance of normal cells to the variance of the malignant cells. Further it is assumed that $R_{E1} < 1$ and $R_{E2} > 1$. There are several other conditions which are formulated as constraints.

Optimal Programming for Treatment during Drug Administration and its Vacation

The statistical moments derived in the previous section are used to construct the optimization programming problem. Usually, growth rate of malignant cells will be more during drug absence period than the drug presence period. Similarly, the loss rate of malignant cells will be more during drug presence than the drug absence period. These stipulations are considered while formulating the proposed programming problem in this section. The health status is considered to be under control as long as the average number of normal cells is more than average number of malignant cells in the treatment of any cancer patient. In other words, the ratio of average normal to malignant cells shall be more than unity. However, the situation seems to be alarming when the ratio is less than unity. In order to study the cells dynamics in the regimen period and vacation periods of drug administration, a linear function is defined using a indicator variable for growth, death, migration, mutation, and transformation rates. The growth, migration/transformation and loss rate of cells can be represented as $\beta_{ij}^{*} = \left[a_r \beta_{ijl} + (1 - a_r) \beta_{ijl} \right]$, $\delta_{ij}^{*} = \left[a_r \delta_{ijl} + (1 - a_r) \delta_{ijl} \right]$ and $\tau_{ij}^{*} = \left[a_r \tau_{ijl} + (1 - a_r) \tau_{ijl} \right]$ respectively. In this situation, we can define $R_{E_1}^{*}$ such that,

$$R_{E_1}^{*} = \frac{\text{Average number of normal cells}}{\text{Average number of malignant cells}}$$

From the derived results of Chapter –IV, it can be redefined as

$$R_{E_1}^{*} = \left\{ \left[N_0 \, e^{A^{*} t} \right] / \left[\frac{\tau_{12}^{*} N_0 e^{At}}{\left(A^{*} - B^{*} \right)} + \left(M_0 - \frac{\tau_{11}^{*} N_0}{\left(A^{*} - B^{*} \right)} \right) e^{B^{*} t} \right] \right\} \tag{5.1}$$

Thus, the objective is to maximize $R_{E_1}^{*}$.

The low fluctuations in the average number of normal cells in any organ is an indicator of consistency in health status. The lower the volatility in the sizes of normal and healthy cells is the greater the indication of the health of the patient. However, a contrary situation will be prevailing in the case of mutant or malignant cells. The increased volatility is desired in this case. Keeping such issues in mind the other program is formulated with the objective function ($R_{E_2}^{*}$) as the ratio between variance of normal cells to that of malignant cells.

$$R_{E_2}^{*} = \frac{\text{Variance of number of normal cells}}{\text{Variance of number of malignant cells}}$$

The results derived previously have defined the objective function as

$$R^*_{E_2} = \left\{\frac{D^*N_0e^{A^*t}}{A^*}\left(e^{A^*t}-1\right)\right\} / \left\{\frac{\tau^*_{11}N_0e^{A^*t}}{\left(A^*-2B^*\right)}+\left(F^*+2E^*\right)\left\{\frac{\tau^*_{11}N_0e^{A^*t}}{\left(A^*-2B^*\right)\left(A-B^*\right)}-\left(M_0-\frac{\tau^*_{11}N_0}{\left(A^*-B^*\right)}\right)\frac{e^{B^*t}}{B^*}\right\}\right.$$
$$+\tau^*_{11}\left\{\begin{array}{l}\dfrac{\tau^*_{11}N_0D^*}{A^*}\left(\dfrac{e^{2A^*t}}{2\left(A^*-B^*\right)^2}+\dfrac{e^{A^*t}}{\left(A^*-2B^*\right)B^*}\right)-\dfrac{\left(E^*-\tau^*_{11}\right)N_0e^{A^*t}}{\left(A^*-2B^*\right)B^*}\\ -\left(\dfrac{\tau^*_{11}N_0D^*-\left(A^*-B^*\right)\left(E^*-\tau^*_{11}\right)N_0}{\left(A^*-B^*\right)B^*}\right)\dfrac{e^{\left(A^*+B^*\right)t}}{\left(A^*-B^*\right)}\end{array}\right\}-\left[\frac{\tau^*_{11}N_0}{\left(A^*-2B^*\right)}+\left(F^*+2E^*\right)\right. \tag{5.2}$$
$$\left.\left.\left(\frac{\tau^*_{11}N_0-\left(A^*-2B^*\right)M_0}{2\left(A^*-2B^*\right)\left(A^*-B^*\right)^2B^*}\right)+\tau^{*2}_{11}N_0\left(\frac{2\left(A^*-B^*\right)\left(\tau^*_{11}-E^*\right)+D^*\tau^*_{11}}{2\left(A^*-2B^*\right)\left(A^*-B^*\right)^2}\right)\right]e^{2B^*t}\right\}$$

Thus, the objective is to minimize $R^*_{E_2}$.

For having a healthy status of the patient under treatment, maintaining the average number of normal cells to a value greater than the average number of malignant cells, and minimizing the fluctuations in the average number of normal cells is required. Hence, the growth of normal cells should be in a consistent environment. This implies that the programming problem shall have constraints like $R^*_{E_2} < 1$ and $R^*_{E_2} > 1$.

The presentation of the said constraints with derived results in the previous section are

$$\left[N_0\,e^{A^*t}\right] > \left[\frac{\tau^*_{12}N_0e^{At}}{\left(A^*-B^*\right)}+\left(M_0-\frac{\tau^*_{11}N_0}{\left(A^*-B^*\right)}\right)e^{B^*t}\right] \tag{5.3}$$

and

$$\left\{\frac{D^*N_0e^{A^*t}}{A^*}\left(e^{A^*t}-1\right)\right\} < \left\{\frac{\tau^*_{11}N_0e^{A^*t}}{\left(A^*-2B^*\right)}+\left(F^*+2E^*\right)\left\{\frac{\tau^*_{11}N_0e^{A^*t}}{\left(A^*-2B^*\right)\left(A-B^*\right)}-\left(M_0-\frac{\tau^*_{11}N_0}{\left(A^*-B^*\right)}\right)\frac{e^{B^*t}}{B^*}\right\}\right.$$
$$+\tau^*_{11}\left\{\begin{array}{l}\dfrac{\tau^*_{11}N_0D^*}{A^*}\left(\dfrac{e^{2A^*t}}{2\left(A^*-B^*\right)^2}+\dfrac{e^{A^*t}}{\left(A^*-2B^*\right)B^*}\right)-\dfrac{\left(E^*-\tau^*_{11}\right)N_0e^{A^*t}}{\left(A^*-2B^*\right)B^*}\\ -\left(\dfrac{\tau^*_{11}N_0D^*-\left(A^*-B^*\right)\left(E^*-\tau^*_{11}\right)N_0}{\left(A^*-B^*\right)B^*}\right)\dfrac{e^{\left(A^*+B^*\right)t}}{\left(A^*-B^*\right)}\end{array}\right\}-\left[\frac{\tau^*_{11}N_0}{\left(A^*-2B^*\right)}+\left(F^*+2E^*\right)\right. \tag{5.4}$$
$$\left.\left.\left(\frac{\tau^*_{11}N_0-\left(A^*-2B^*\right)M_0}{2\left(A^*-2B^*\right)\left(A^*-B^*\right)^2B^*}\right)+\tau^{*2}_{11}N_0\left(\frac{2\left(A^*-B^*\right)\left(\tau^*_{11}-E^*\right)+D^*\tau^*_{11}}{2\left(A^*-2B^*\right)\left(A^*-B^*\right)^2}\right)\right]e^{2B^*t}\right\}$$

There are some more additional constraints as below. The average size of normal cells should be within threshold limits. It implies a constraint,

$$L^*_n \le \left[N_0\,e^{A^*t}\right] \le U^*_n \tag{5.5}$$

Average number of malignant cells shall not be more than warning limits. Hence,

$$\left[\frac{\tau^*_{12}N_0e^{At}}{\left(A^*-B^*\right)}+\left(M_0-\frac{\tau^*_{11}N_0}{\left(A^*-B^*\right)}\right)e^{B^*t}\right] \le U^*_m \tag{5.6}$$

The consistency in average number of normal cells should be maintained at a certain level. More volatility in growth of normal cells leads to much complication in the functioning of an organ. Hence, the constraint with the above notion is

$$\left\{\frac{D^*N_0e^{A^*t}}{A^*}\left(e^{A^*t}-1\right)\right\}\le U_{vn}^*. \tag{5.7}$$

The consistency in the growth of malignant cells results in a threat to healthy functioning. So, higher volatility among malignant cells is always desired. Hence, the constraint with the above notion is

$$\begin{aligned}&\left\{\frac{\tau_{11}^*N_0e^{A^*t}}{\left(A^*-2B^*\right)}+\left(F^*+2E^*\right)\left\{\frac{\tau_{11}^*N_0e^{A^*t}}{\left(A^*-2B^*\right)\left(A-B^*\right)}-\left(M_0-\frac{\tau_{11}^*N_0}{\left(A^*-B^*\right)}\right)\frac{e^{B^*t}}{B^*}\right\}\right.\\&+\tau_{11}^*\left\{\frac{\tau_{11}^*N_0D^*}{A^*}\left(\frac{e^{2A^*t}}{2\left(A^*-B^*\right)^2}+\frac{e^{A^*t}}{\left(A^*-2B^*\right)B^*}\right)-\frac{\left(E^*-\tau_{11}^*\right)N_0e^{A^*t}}{\left(A^*-2B^*\right)B^*}\right.\\&\left.\left.-\left(\frac{\tau_{11}^*N_0D^*-\left(A^*-B^*\right)\left(E^*-\tau_{11}^*\right)N_0}{\left(A^*-B^*\right)B^*}\right)\frac{e^{\left(A^*+B^*\right)t}}{\left(A^*-B^*\right)}\right\}\right.\\&-\left[\frac{\tau_{11}^*N_0}{\left(A^*-2B^*\right)}+\left(F^*+2E^*\right)\left(\frac{\tau_{11}^*N_0-\left(A^*-2B^*\right)M_0}{2\left(A^*-2B^*\right)\left(A^*-B^*\right)^2B^*}\right)\right.\\&\left.\left.+\tau_{11}^{*2}N_0\left(\frac{2\left(A^*-B^*\right)\left(\tau_{11}^*-E^*\right)+D^*\tau_{11}^*}{2\left(A^*-2B^*\right)\left(A^*-B^*\right)^2}\right)\right]e^{2B^*t}\right\}\ge L_{vm}^*\end{aligned} \tag{5.8}$$

Where,

$$A^*=\beta_{11}^*-\tau_{11}^*-\delta_{11}^* \qquad B^*=\beta_{21}^*-\delta_{21}^*-\tau_{21}^* \qquad D^*=\beta_{11}^*+\tau_{11}^*+\delta_{11}^*$$

$$E^*=\beta_{32}^*-\delta_{32}^*-\tau_{32}^* \qquad F^*=\beta_{21}^*+\delta_{21}^*+\tau_{21}^* \qquad -$$

$$\beta_{11}^*=a_1\beta_{111}+(1-a_1)\beta_{110} \qquad \tau_{11}^*=a_2\tau_{111}+(1-a_2)\tau_{110} \qquad \beta_{21}^*=a_3\beta_{211}+(1-a_3)\beta_{210}$$

$$\beta_{32}^*=a_4\beta_{321}+(1-a_4)\beta_{320} \qquad \delta_{11}^*=a_5\delta_{111}+(1-a_5)\delta_{110} \qquad \delta_{21}^*=a_6\delta_{211}+(1-a_6)\delta_{210}$$

$$\tau_{21}^*=a_7\tau_{211}+(1-a_7)\tau_{210} \qquad \delta_{32}^*=a_8\delta_{321}+(1-a_8)\delta_{320} \qquad \tau_{32}^*=a_9\tau_{321}+(1-a_9)\tau_{320}$$

N_0 - Initial number of normal cells in an organ

M_0 - Initial number of malignant cells in an organ

L_n^*, U_n^* - Lower and upper threshold limits of the number of normal cells

U_m^* - Warning upper limit on the average number of malignant cells

U_{vn}^* - Upper allowable limit on the volatility of number of normal cells

L_{vm}^* - desired lower limit on the volatility of malignant cells

The non-negative decision parameters under study are $\beta_{11}^*\ge 0$, $\tau_{11}^*\ge 0$, $\delta_{11}^*\ge 0$, $\beta_{21}^*\ge 0$, $\tau_{21}^*\ge 0$, $\delta_{21}^*\ge 0$, $\beta_{32}^*\ge 0$, $\tau_{32}^*\ge 0$, $\delta_{32}^*\ge 0$.

6. Sensitivity Analysis with Optimization Models

This section consists of four sets of programming problems addressing the issues of (i) maximizing $R_{E_1}^*$ during drug vacation period; (ii) maximizing $R_{E_1}^*$ during drug administration period; (iii) minimizing $R_{E_2}^*$ during drug vacation period and (iv) minimizing $R_{E_2}^*$ during drug administration period under the well-defined subjective constraints.

Optimization problem of maximizing $R_{E_1}^*$ During Drug Vacation Period

The illustration has been presented here for aforementioned problems. The indicator function is defined for denoting the drug administration (presence of drug) and vacation periods (absence of drug). The results are obtained by solving the objective function in (5.1) and the set of constraints from (5.3) to (5.8) by considering the indicator variable as drug vacation period (absence of drug).

The optimal solutions pertaining to local maximization are obtained as the formulated programming problem is non-linear. The results are presented in terms of the values of decision parameter and corresponding objective function. While exploring the estimated values of parameters, it is considered for varying values of L_n^*, U_n^*, U_m^*, U_{vn}^*, L_{vm}^*, M_0, N_0, t, one at a time, when the remaining are fixed values of other target limits. From the appendix V(c), it is observed that the objectives function $R_{E_1}^*$ is an increasing function of N_0, L_n^*, U_n^*, and decreasing functions of M_0, t. β_{110} and δ_{110} are increasing functions of N_0. When increasing M_0: $\beta_{110} < \delta_{110}$, $\beta_{210} > (\delta_{210}$ & $\tau_{210})$ and $\beta_{210} > (\beta_{110}, \beta_{320})$; β_{110}, δ_{110} are decreasing functions of L_n^*. When increasing L_n^*: $\beta_{210} > (\beta_{110}, \beta_{320})$. When increasing U_n^*: β_{110}, δ_{110} and δ_{210} are decreasing functions of U_n^*. When increasing U_m^* : $\beta_{110} < \delta_{110}$ and invariant, $\beta_{110} < (\beta_{210}, \beta_{320})$. When increasing U_{vn}^*: $\beta_{110} < \delta_{110}$, $\beta_{110} < (\beta_{210}, \beta_{320})$. When increasing U_{vn}^*: $\beta_{110} < \delta_{110}$, $\delta_{210} > (\beta_{210}, \tau_{210})$, $\beta_{110} < (\beta_{210}, \beta_{320})$. When increasing t: $\beta_{110} < \delta_{110}$, $\beta_{210} < (\beta_{110}, \beta_{320})$ and $\beta_{210} < \delta_{210}$.

Optimization problem of Maximizing $R_{E_1}^*$ during drug administration period

An illustration has been presented here for aforementioned problems. The results are obtained by solving objective function in (5.1) with a set of constraints from (5.3) to (5.8) under consideration with the indicator variable in the drug administration period (presence of drug). Since the programming problem handled here is non-linear it has only a local optimum solution. The results of the sensitivity analysis of the problem are given in the tables from Annexure 3(a) & 3(b). The results are presented in terms of the values of the decision parameter and corresponding objective function. While exploring the estimated values of parameters, varying values of L_n^*, U_n^*, U_m^*, U_{vn}^*, L_{vm}^*, M_0, N_0, t one at a time is considered when the remaining are fixed values of other target limits.

From the appendix – V (d), it is observed that the objective function $R_{E_1}^*$ is an increasing function of N_0, U_m^*, U_{vn}^*, are decreasing function of M_0, L_n^* and t. When increasing N_0: $\beta_{111} < \delta_{111}$, $\beta_{211} > (\delta_{211}, \tau_{211})$, $\beta_{211} > (\beta_{111}, \beta_{321})$. When increasing M_0: $\beta_{111} < \delta_{111}$, $\beta_{211} > (\beta_{111}, \beta_{321})$. δ_{111} is a decreasing function of L_n^*. When increasing L_n^*: $\beta_{211} > (\delta_{211}, \tau_{211})$ and $\beta_{211} > \beta_{321}$. When increasing U_n^*: β_{111}, δ_{111} and $\beta_{211} > \delta_{211}$. When increasing U_m^* : $\beta_{111} < \delta_{111}$, $\beta_{211} > (\beta_{111}, \beta_{321})$ and $\beta_{211} > (\beta_{321}, \tau_{211})$. When increasing U_{vn}^*: $\beta_{111} < \delta_{111}$, $(\beta_{111}, \beta_{211}) > \beta_{321}$. When increasing L_{vm}^*: $\beta_{111} < \delta_{111}$, $\beta_{211} > (\beta_{321}, \tau_{211})$ and $\beta_{211} > (\beta_{111}, \beta_{321})$. When increasing t: $\beta_{111} < \delta_{111}$ and $\beta_{211} > (\beta_{111}, \beta_{321})$.

Optimization problem of minimizing $R_{E_2}^*$ during drug vacation period

The illustration given here is for discussing the situation of cancer growth related issues during the drug vacation period. The indicator variable is considered with drug vacation period (absence of drug). The results are obtained by solving objective function in (5.2) with the formulated constraints given from (5.3) to (5.8). This illustration has given local optimal results only as the formulated programming problem is nonlinear. The results are presented in terms of the values of the decision parameter and corresponding objective function. While exploring the estimated values of parameters, varying values of L_n^*, U_n^*, U_m^*, U_{vn}^*, L_{vm}^*, M_0, N_0, t is considered, when the remaining are fixed values of other target limits.

From the appendix –V (e), it is observed that the objective function $R_{E_2}^*$ is an increasing function of M_0, and decreasing function of U_{vn}^*. When increasing N_0: $\beta_{110} < (\delta_{110}, \tau_{110})$, $\beta_{210} > (\beta_{110}, \beta_{320})$ and $\beta_{210} > (\delta_{210}, \tau_{210})$. β_{110}, δ_{110} are decreasing functions of M_0. When increasing M_0 : $\beta_{110} < (\delta_{110}, \tau_{110})$, $(\beta_{110}, \beta_{210}) < \beta_{320}$ and $(\delta_{110}, \delta_{210}) > \delta_{320}$. β_{110} and τ_{210} are decreasing functions of L_n^*. When increasing L_n^* : $\beta_{110} < (\delta_{110}, \tau_{110})$, $(\beta_{110}, \beta_{210}) < \beta_{320}$ and $\tau_{210} > \tau_{320}$. When increasing U_m^* : $\beta_{110} < (\delta_{110}, \tau_{110})$ and $\beta_{210} > (\beta_{110}, \beta_{320})$. When increasing U_{vn}^*: $\beta_{110} < (\delta_{110}, \tau_{110})$, $(\beta_{110}, \beta_{210}) < \beta_{320}$, $(\beta_{210}, \delta_{210}) < \tau_{110}$, $\tau_{210} > \tau_{320}$ and δ_{210}, δ_{320}. When increasing L_{vm}^* : $\beta_{110} < (\delta_{110}, \tau_{110})$, $\beta_{110} < (\beta_{210}, \beta_{320})$, $\beta_{210} > \delta_{210}$. δ_{210} is a decreasing function of t. When increasing t : $\beta_{110} < (\delta_{110}, \tau_{110})$ and $\beta_{110} < (\beta_{210}, \beta_{320})$.

Optimization problem of minimizing $R_{E_2}^*$ during drug administration period

The given illustration here considers the minimization of $R_{E_2}^*$ during the drug administration period. The indicator variable has been functioned with the stipulation of drug presence. The results are obtained by solving the objective function in (5.2) along with developed constraints given in (5.3) through (5.8) Results are presented for local optimality only as the developed problem is nonlinear in nature. The results of the sensitivity analysis of the problem are given in the tables from Annexure 3(c) & 3(d). The results are presented in term of the values of decision parameter and corresponding objective function. While exploring the estimated values of parameters, varying values of L_n^*, U_n^*, U_m^*, U_{vn}^*, L_{vm}^*, M_0, N_0, t, one at a time when the remaining are fixed values of other target limits.

From the appendix V(f), it is observed that the objective function $R_{E_2}^*$ is an increasing function of M_0, and decreasing function of L_n^* and t. When increasing N_0: $\delta_{111} > (\beta_{111}, \tau_{111})$, $(\beta_{111}, \beta_{211}) < \beta_{321}$, $\tau_{211} < \tau_{321}$. δ_{111} is an increasing function of M_0. When increasing M_0: $\delta_{111} > (\beta_{111}, \tau_{111})$, $(\beta_{211}, \delta_{211}) < \tau_{211}$, $\beta_{211} < \beta_{321}$, $(\beta_{321}, \delta_{321}) < \tau_{321}$ and $(\beta_{111}, \beta_{211}) < \beta_{321}$. β_{111}, δ_{111} and τ_{111} are decreasing functions of L_n^*. When increasing L_n^* : $(\beta_{211}, \delta_{211}) < \tau_{211}$, $(\beta_{111}, \beta_{211}) < \beta_{321}$ and $\tau_{211} < \tau_{321}$. δ_{111} is a decreasing function of U_n^*. When increasing U_n^*: $\delta_{111} > (\beta_{111}, \tau_{111})$, $(\beta_{111}, \beta_{211}) < \beta_{321}$, and $\delta_{211} < \delta_{321}$. When increasing U_m^*: $\delta_{111} > (\beta_{111}, \tau_{111})$, $\beta_{111} < \beta_{211}$, $\beta_{211} < \beta_{321}$ and $\tau_{211} > \tau_{321}$. β_{111}, δ_{111} are increasing functions of U_{vn}^* and δ_{211}, τ_{111}, τ_{211} are decreasing functions of U_{vn}^*. When increasing U_{vn}^*: β_{111}, $< (\delta_{111}, \tau_{111})$ and $(\beta_{111}, \beta_{211}) < \beta_{321}$. δ_{111} is a decreasing function of t.

Summary of Optimal Drug Administration

This section deals with a set of non-linear optimization programming problems which are constructed with the derived mathematical relations for different statistical measures and there by defined relative efficiency such as average number of normal cells, average number of malignant cells, variance of number of normal cells and variance of number of malignant cells, etc. The decision parameters involved in the cell division dynamics such as growth rate of normal cells, death rate of normal cells, transformation rate (normal cells to malignant cells), growth rate of malignant cells, death rate of malignant cells, migration rate of malignant cells, growth rate of immigrant malignant cells, death rate of immigrant malignant cells and emigration rate of malignant cells are predicted and presented in a table. The discussions regarding the predicted parameters are also presented. The problems in this chapter are dealt with separately and solved. The scope of this programming can be extended with the goal programming problem approach for dealing the multi objective nonlinear programming problems.

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Annexure –IV (a)

Table for all statistical measures with varying values of one parameter when other parameters are fixed drug vacation period.

N_0	M_0	β_{110}	τ_{110}	β_{210}	β_{320}	δ_{110}	δ_{210}	τ_{210}	δ_{320}	τ_{320}	t	$m^*_{1,0}(t)$	$m^*_{0,1}(t)$	$m^*_{2,0}(t)$	$m^*_{0,2}(t)$	$m^*_{1,1}(t)$	r (n, m)
400	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	890.2164	253641.5	436.3986	7.12E+07	27683.67	0.1571
800	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	1780.4327	260908.6	872.7973	7.15E+07	55367.33	0.2216
1200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	2670.6491	268175.6	1309.196	7.21E+07	83051	0.2704
1600	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	3560.8655	275442.6	1745.595	7.25E+07	110734.7	0.3113
2000	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	4451.0819	282709.6	2181.993	7.29E+07	138418.3	0.3470
200	**1000**	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	496382.5	218.1993	1.42E+08	13841.83	0.0787
200	**1200**	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	594932.4	218.1993	1.70E+08	13841.83	0.0719
200	**1300**	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	644207.3	218.1993	1.84E+08	13841.83	0.0690
200	**1400**	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	693482.2	218.1993	1.98E+08	13841.83	0.0665
200	**1500**	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	742757.1	218.1993	2.12E+08	13841.83	0.0643
200	500	**1.2**	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	664.0234	305526.6	462.1836	1.01E+08	20794.15	0.0964
200	500	**1.4**	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	990.6065	305896.6	978.9749	1.00E+08	31269.26	0.0997
200	500	**1.6**	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	1477.8112	306326.7	2077.2	1.00E+08	47077.16	0.1031
200	500	**1.8**	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	2204.6353	306830.7	4419.49	1.00E+08	70978.65	0.1067
200	500	**2.0**	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	3288.9294	307427	9433.608	9.98E+07	107202.8	0.1105
200	500	1.0	**0.2**	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	364.4238	309198.7	339.5462	1.01E+08	5686.589	0.0307
200	500	1.0	**0.4**	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	244.2806	316422.5	411.0414	1.07E+08	–1976.5	–0.0094
200	500	1.0	**0.6**	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	163.7462	322778	373.995	8.85E+07	–3477.97	–0.0191
200	500	1.0	**0.7**	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	134.0640	325676.8	340.3263	9.25E+07	–3164.79	–0.0178
200	500	1.0	**0.8**	4.0	0.3	0.5	0.5	0.3	0.03	0.01	2.0	109.7623	328410.3	303.744	9.34E+07	–2530.78	–0.0150
200	500	1.0	0.1	**4.1**	0.3	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	372601.9	218.1993	1.48E+08	16381.28	0.0910
200	500	1.0	0.1	**4.2**	0.3	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	454894.5	218.1993	2.19E+08	19404.52	0.0888
200	500	1.0	0.1	**4.3**	0.3	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	555377.3	218.1993	3.23E+08	23005.84	0.0866
200	500	1.0	0.1	**4.4**	0.3	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	678072.9	218.1993	4.77E+08	27298.23	0.0846
200	500	1.0	0.1	**4.5**	0.3	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	827893.8	218.1993	7.04E+08	32417.08	0.0827
200	500	1.0	0.1	4.0	**0.4**	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	305205.5	218.1993	1.04E+08	22199.37	0.1470
200	500	1.0	0.1	4.0	**0.5**	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	305205.5	218.1993	1.08E+08	30556.9	0.1989
200	500	1.0	0.1	4.0	**0.6**	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	305205.5	218.1993	1.12E+08	38914.43	0.2490
200	500	1.0	0.1	4.0	**0.7**	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	305205.5	218.1993	1.16E+08	47271.96	0.2975
200	500	1.0	0.1	4.0	**0.8**	0.5	0.5	0.3	0.03	0.01	2.0	445.1082	305205.5	218.1993	1.19E+08	55629.5	0.3446
200	500	1.0	0.1	4.0	0.3	**0.6**	0.5	0.3	0.03	0.01	2.0	364.4238	305060.6	169.7731	1.01E+08	11343.37	0.0867
200	500	1.0	0.1	4.0	0.3	**0.7**	0.5	0.3	0.03	0.01	2.0	298.3649	304924.9	132.0689	1.01E+08	9295.286	0.0806
200	500	1.0	0.1	4.0	0.3	**0.8**	0.5	0.3	0.03	0.01	2.0	244.2806	304797.5	102.7603	1.01E+08	7616.544	0.0748
200	500	1.0	0.1	4.0	0.3	**1.0**	0.5	0.3	0.03	0.01	2.0	163.7462	304565.1	62.3325	1.01E+08	5113.068	0.0645

N_0	M_0	β_{110}	τ_{110}	β_{210}	β_{320}	δ_{110}	δ_{210}	τ_{210}	δ_{320}	τ_{320}	t	$m^*_{1,0}(t)$	$m^*_{0,1}(t)$	$m^*_{2,0}(t)$	$m^*_{0,2}(t)$	$m^*_{1,1}(t)$	r (n, m)
200	500	1.0	0.1	4.0	0.3	**1.1**	0.5	0.3	0.03	0.01	2.0	134.0640	304458.8	48.618	1.01E+08	4189.035	0.0598
200	500	1.0	0.1	4.0	0.3	0.5	**0.6**	0.3	0.03	0.01	2.0	445.1082	250008	208.1993	7.10E+07	11707.44	0.0963
200	500	1.0	0.1	4.0	0.3	0.5	**0.7**	0.3	0.03	0.01	2.0	445.1082	204800.6	208.1993	5.00E+07	9912.341	0.0971
200	500	1.0	0.1	4.0	0.3	0.5	**0.8**	0.3	0.03	0.01	2.0	445.1082	167774.4	208.1993	3.53E+07	8401.583	0.0980
200	500	1.0	0.1	4.0	0.3	0.5	**0.9**	0.3	0.03	0.01	2.0	445.1082	137448.2	208.1993	2.49E+07	7129.236	0.0990
200	500	1.0	0.1	4.0	0.3	0.5	**1.0**	0.3	0.03	0.01	2.0	445.1082	112609.1	208.1993	1.76E+07	6056.891	0.1000
200	500	1.0	0.1	4.0	0.3	0.5	0.5	**0.4**	0.03	0.01	2.0	445.1082	250008	208.1993	7.10E+07	11707.44	0.0963
200	500	1.0	0.1	4.0	0.3	0.5	0.5	**0.5**	0.03	0.01	2.0	445.1082	204800.6	208.1993	5.00E+07	9912.341	0.0971
200	500	1.0	0.1	4.0	0.3	0.5	0.5	**0.6**	0.03	0.01	2.0	445.1082	167774.4	208.1993	3.53E+07	8401.583	0.0980
200	500	1.0	0.1	4.0	0.3	0.5	0.5	**0.7**	0.03	0.01	2.0	445.1082	137448.2	208.1993	2.49E+07	7129.236	0.0990
200	500	1.0	0.1	4.0	0.3	0.5	0.5	**0.8**	0.03	0.01	2.0	445.1082	112609.1	208.1993	1.76E+07	6056.891	0.1000
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	**0.04**	0.01	2.0	445.1082	250008	218.1993	7.07E+07	13006.08	0.1047
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	**0.06**	0.01	2.0	445.1082	250008	218.1993	7.02E+07	11334.57	0.0916
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	**0.08**	0.01	2.0	445.1082	250008	218.1993	6.97E+07	9663.066	0.0784
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	**0.10**	0.01	2.0	445.1082	250008	218.1993	6.92E+07	7991.56	0.0651
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	**0.12**	0.01	2.0	445.1082	250008	218.1993	6.86E+07	6320.053	0.0516
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	**0.02**	2.0	445.1082	250008	218.1993	7.07E+07	13006.08	0.1047
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	**0.03**	2.0	445.1082	250008	218.1993	7.05E+07	12170.33	0.0981
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	**0.04**	2.0	445.1082	250008	218.1993	7.02E+07	11334.57	0.0916
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	**0.05**	2.0	445.1082	250008	218.1993	6.99E+07	10498.82	0.0850
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	**0.06**	2.0	445.1082	250008	218.1993	6.97E+07	9663.066	0.0784
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	**3.0**	664.0234	5.55E+06	6.16E+02	3.50E+10	5.08E+05	0.1094
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	**3.2**	914.4451	1.03E+07	7.47E+02	1.21E+11	1.04E+06	0.1094
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	**3.4**	719.3280	1.92E+07	9.03E+02	4.18E+11	2.14E+06	0.1101
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	**3.6**	779.2387	3.57E+07	1.09E+03	1.44E+12	4.40E+06	0.1111
200	500	1.0	0.1	4.0	0.3	0.5	0.5	0.3	0.03	0.01	**3.8**	844.1392	6.63E+07	1.31E+03	4.99E+12	9.04E+06	0.1118

Annexure –IV (b)

Table for all statistical measures with varying values of one parameter when other parameters are fixed, during drug administration period

N_0	M_0	β_{111}	τ_{111}	β_{211}	β_{321}	δ_{111}	δ_{211}	τ_{211}	δ_{321}	τ_{321}	t	$m^*_{1,0}(t)$	$m^*_{0,1}(t)$	$m^*_{2,0}(t)$	$m^*_{0,2}(t)$	$m^*_{1,1}(t)$	r (n, m)
400	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	2.0	17526.42	580.28	8377.613	1302.274	–341.512	–0.10339
800	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	35052.83	670.46	16755.23	1292.301	–683.024	–0.14678
1200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	52579.25	760.641	25132.84	1282.328	–1024.54	–0.18047
1600	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	70105.67	850.822	33510.45	1272.355	–1366.05	–0.2092
2000	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	87632.08	941.003	41888.07	1262.383	–1707.56	–0.23482
200	**600**	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	633.2096	4188.807	1569.71	–170.756	–0.06659
200	**1000**	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	1025.289	4188.807	2619.507	–170.756	–0.05155
200	**1200**	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	1221.329	4188.807	3144.406	–170.756	–0.04705
200	**1600**	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	1613.408	4188.807	4194.203	–170.756	–0.04074
200	**2000**	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	2005.807	4188.807	5244.001	–170.756	–0.03643
200	500	**2.1**	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	10703.41	542.6362	6242.541	1301.313	–204.265	–0.07167
200	500	**2.3**	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	15967.61	561.7883	13853.15	1282.911	–288.293	–0.06838
200	500	**2.5**	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	23820.87	588.5361	30723.18	1251.576	–395.97	–0.06386
200	500	**2.7**	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	35536.56	626.0244	68120.26	1199.731	–519.642	–0.05748
200	500	**2.9**	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	53014.32	678.7361	151034.9	1115.636	–626.604	–0.04827
200	500	2.0	**0.02**	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8589.685	578.921	8126.451	1217.76	–278.82	–0.08863
200	500	2.0	**0.03**	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8419.598	621.3263	11824.18	1047.366	–345.146	–0.09808
200	500	2.0	**0.04**	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8252.879	662.4381	15292.82	799.5986	–372.817	–0.10661
200	500	2.0	**0.05**	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8089.461	702.2881	18542.73	477.3662	–364.757	–0.1226
200	500	2.0	**0.06**	1.0	0.100	0.1	1.0	0.01	0.10	0.001	1.0	7929.279	740.9071	21583.9	85.5232	–323.794	–0.23832
200	500	2.0	0.10	**0.8**	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	369.6272	4188.807	848.6954	–138.915	–0.07368
200	500	2.0	0.10	**1.2**	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	780.9702	4188.807	2253.43	–212.544	–0.06918
200	500	2.0	0.10	**1.4**	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	1146.249	4188.807	3916.095	–267.83	–0.06613
200	500	2.0	0.10	**1.6**	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	1689.59	4188.807	7081.028	–341.537	–0.06271
200	500	2.0	0.10	**1.8**	0.100	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	2498.316	4188.807	13076.97	–440.502	–0.05952
200	500	2.0	0.10	1.0	**0.006**	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	535.1897	4188.807	785.877	–1801.87	–0.99312
200	500	2.0	0.10	1.0	**0.008**	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	535.1897	4188.807	796.9703	–1767.17	–0.96719
200	500	2.0	0.10	1.0	**0.010**	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	535.1897	4188.807	808.0635	–1732.46	–0.94167
200	500	2.0	0.10	1.0	**0.012**	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	535.1897	4188.807	819.1568	–1697.76	–0.91653
200	500	2.0	0.10	1.0	**0.014**	0.1	1.0	0.01	0.10	0.001	1.0	8763.208	535.1897	4188.807	830.2501	–1663.55	–0.89205
200	500	2.0	0.10	1.0	0.100	**0.2**	1.0	0.01	0.10	0.001	1.0	7174.708	528.8697	3089.154	1311.606	–140.858	–0.06998
200	500	2.0	0.10	1.0	0.100	**0.4**	1.0	0.01	0.10	0.001	1.0	4809.351	518.9325	1680.027	1316.927	–95.6889	–0.06433
200	500	2.0	0.10	1.0	0.100	**0.6**	1.0	0.01	0.10	0.001	1.0	3223.804	511.7262	915.2043	1319.26	–64.8721	–0.05904
200	500	2.0	0.10	1.0	0.100	**0.8**	1.0	0.01	0.10	0.001	1.0	2160.981	506.4738	500.3265	1319.802	–43.9019	–0.05403
200	500	2.0	0.10	1.0	0.100	**1.0**	1.0	0.01	0.10	0.001	1.0	1448.549	502.6244	274.9412	1319.265	–29.6655	–0.04926

N_0	M_0	β_{111}	τ_{111}	β_{211}	β_{321}	δ_{111}	δ_{211}	τ_{211}	δ_{321}	τ_{321}	t	$m^*_{1,0}(t)$	$m^*_{0,1}(t)$	$m^*_{2,0}(t)$	$m^*_{0,2}(t)$	$m^*_{1,1}(t)$	r (n, m)
200	500	2.0	0.10	1.0	0.100	0.1	**1.1**	0.01	0.10	0.001	1.0	8763.208	444.2729	4188.807	1170.627	–153.773	–0.06944
200	500	2.0	0.10	1.0	0.100	0.1	**1.2**	0.01	0.10	0.001	1.0	8763.208	369.6272	4188.807	1028.855	–138.915	–0.06692
200	500	2.0	0.10	1.0	0.100	0.1	**1.3**	0.01	0.10	0.001	1.0	8763.208	308.3159	4188.807	913.0742	–125.89	–0.06437
200	500	2.0	0.10	1.0	0.100	0.1	**1.4**	0.01	0.10	0.001	1.0	8763.208	257.9338	4188.807	818.5052	–114.445	–0.06181
200	500	2.0	0.10	1.0	0.100	0.1	**1.5**	0.01	0.10	0.001	1.0	8763.208	216.5103	4188.807	740.8735	–104.367	–0.05924
200	500	2.0	0.10	1.0	0.100	0.1	1.0	**0.30**	0.10	0.001	1.0	8763.208	313.9193	4188.807	923.6197	–127.118	–0.06463
200	500	2.0	0.10	1.0	0.100	0.1	1.0	**0.40**	0.10	0.001	1.0	8763.208	262.5393	4188.807	827.1362	–115.525	–0.06206
200	500	2.0	0.10	1.0	0.100	0.1	1.0	**0.50**	0.10	0.001	1.0	8763.208	220.298	4188.807	747.9785	–105.319	–0.0595
200	500	2.0	0.10	1.0	0.100	0.1	1.0	**0.60**	0.10	0.001	1.0	8763.208	185.5488	4188.807	682.6326	–96.3117	–0.05696
200	500	2.0	0.10	1.0	0.100	0.1	1.0	**0.70**	0.10	0.001	1.0	8763.208	156.9428	4188.807	628.3201	–88.3447	–0.05446
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	**0.02**	0.001	1.0	8763.208	535.1897	4188.807	1750.991	1217.429	0.449528
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	**0.04**	0.001	1.0	8763.208	535.1897	4188.807	1640.058	870.3828	0.332074
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	**0.06**	0.001	1.0	8763.208	535.1897	4188.807	1529.126	523.3347	0.206782
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	**0.08**	0.001	1.0	8763.208	535.1897	4188.807	1418.193	176.2902	0.072329
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	**0.12**	0.001	1.0	8763.208	535.1897	4188.807	1196.328	–517.802	–0.23131
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	**0.002**	1.0	8763.208	535.1897	4188.807	1301.714	–188.109	–0.08056
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	**0.004**	1.0	8763.208	535.1897	4188.807	1290.621	–222.813	–0.09583
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	**0.006**	1.0	8763.208	535.1897	4188.807	1279.527	–257.518	–0.11123
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	**0.008**	1.0	8763.208	535.1897	4188.807	1268.434	–292.222	–0.12678
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	**0.01**	1.0	8763.208	535.1897	4188.807	1257.341	–326.927	–0.14246
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	**2.5**	22546.1	605.292	28123.14	1623.921	–470.497	–0.06962
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	**3.0**	58006.91	789.5008	187176	1932.266	–919.701	–0.04836
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	**3.5**	149240.9	1267.265	1241607	2222.675	831.3823	0.015826
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	**4.0**	383969.1	2500.273	8225398	2467.901	26563.17	0.186439
200	500	2.0	0.10	1.0	0.100	0.1	1.0	0.01	0.10	0.001	**4.5**	987880.8	5676.365	54464291	2591.531	238355.3	0.63444

Appendix-3(a)

Table: Values of R_{E1}*, β_{11}, τ_{11}, δ_{11}, β_{21},δ_{21}, τ_{21}, β_{32}, δ_{32}, τ_{32} for Varying values of one value of the following N_0, M_0, L_n, U_n, U_m,U_{vn}, L_{vm}, t when other parameters are constants (Drug Administration Period)

N_0	M_0	L_n	U_n	U_m	U_{vn}	L_{nm}	t	R_{E1}^*	β_{11}	β_{21}	δ_{11}	τ_{11}	δ_{21}	τ_{21}	β_{32}	δ_{32}	τ_{32}
900000	15000	15000	100000	20000	20000	2000	5.0	32.1683	0.0000	0.0000	1.0236	1.21E+06	6.09E+05	6.05E+05	6.09E+05	0.0000	0.0000
1000000	15000	15000	100000	20000	20000	2000	5.0	37.3954	0.0000	0.0000	1.0499	1.00E+06	5.09E+05	4.98E+05	5.09E+05	0.0000	0.0000
1100000	15000	15000	100000	20000	20000	2000	5.0	42.6861	0.2222	0.0000	1.2626	9.87E+06	4.98E+06	4.98E+06	5.00E+06	0.0000	0.0000
1500000	15000	15000	100000	20000	20000	2000	5.0	64.3578	0.0000	0.0000	1.8967	1.27E+06	6.43E+05	6.43E+05	6.43E+05	0.0000	0.0000
1600000	15000	15000	100000	20000	20000	2000	5.0	69.8791	0.2376	0.0000	2.1168	0.00E+00	7.38E-01	3.89E-01	2.12E+07	0.0000	0.0000
1000000	**10000**	15000	100000	20000	20000	2000	5.0	56.0931	0.2184	0.0000	1.2356	5.29E+06	2.71E+06	2.71E+06	2.70E+06	0.0000	0.0000
1000000	**12000**	15000	100000	20000	20000	2000	5.0	46.7442	0.2184	0.0000	1.2356	1.18E+06	5.98E+05	5.98E+05	5.97E+05	0.0000	0.0000
1000000	**13000**	15000	100000	20000	20000	2000	5.0	43.1485	0.0000	0.0000	1.0499	5.25E+06	5.24E+06	8.40E-01	1.44E+06	0.0000	0.0000
1000000	**16000**	15000	100000	20000	20000	2000	5.0	35.0582	0.2892	0.0000	1.2356	3.64E+06	2.10E+01	3.60E+06	3.64E+06	0.0000	0.0000
1000000	**18000**	15000	100000	20000	20000	2000	5.0	31.1628	0.2184	0.0000	1.2356	5.27E+06	2.66E+06	2.66E+06	2.67E+06	0.0000	0.0000
1000000	15000	**9000**	100000	20000	20000	2000	5.0	44.1474	0.0000	0.0000	1.1776	4.17E+06	2.10E+06	2.09E+06	2.10E+06	0.0000	0.0000
1000000	15000	**9500**	100000	20000	20000	2000	5.0	43.5187	0.0000	0.0000	1.1641	1.57E+06	8.00E+05	7.83E+05	8.00E+05	0.0000	0.0000
1000000	15000	**10000**	100000	20000	20000	2000	5.0	42.9052	0.0000	0.0000	1.1513	2.69E+06	1.35E+06	1.34E+06	1.35E+06	0.0000	0.0000
1000000	15000	**10500**	100000	20000	20000	2000	5.0	42.3057	0.0000	0.0000	1.1391	2.44E+06	1.24E+06	1.22E+06	1.24E+06	0.0000	0.0000
1000000	15000	**11000**	100000	20000	20000	2000	5.0	41.7191	0.0000	0.0000	1.1275	2.60E+06	1.31E+06	1.30E+06	1.31E+06	0.0000	0.0000
1000000	15000	15000	**19900**	20000	20000	2000	5.0	37.3954	0.1878	0.0000	1.2356	3.62E+06	2.02E-01	3.56E+06	3.62E+06	0.0000	0.0000
1000000	15000	15000	**20000**	20000	20000	2000	5.0	37.3954	0.1874	0.0000	1.2356	9.53E+06	4.82E+06	4.76E+06	4.88E+06	0.0000	0.0000
1000000	15000	15000	**20100**	20000	20000	2000	5.0	37.3954	0.1870	0.0000	1.2356	9.18E+05	4.62E+05	4.62E+05	4.62E+05	0.0000	0.0000
1000000	15000	15000	**20200**	20000	20000	2000	5.0	37.3954	0.1865	0.0000	1.2356	9.10E+05	4.64E+05	4.54E+05	4.64E+05	0.0000	0.0000
1000000	15000	15000	**20400**	20000	20000	2000	5.0	37.3954	0.1857	0.0000	1.2356	2.30E+06	1.16E+06	1.15E+06	1.16E+06	0.0000	0.0000
1000000	15000	15000	25000	**20100**	20000	2000	5.0	37.3954	0.0000	0.0000	1.0499	1.00E+06	5.09E+05	4.98E+05	5.09E+05	0.0000	0.0000
1000000	15000	15000	25000	**20800**	20000	2000	5.0	37.3954	0.2184	0.0000	1.2356	1.45E+06	7.34E+05	7.34E+05	7.34E+05	0.0000	0.0000
1000000	15000	15000	25000	**23000**	20000	2000	5.0	37.3954	0.2184	0.0000	1.2356	1.36E+06	6.93E+05	6.81E+05	6.93E+05	0.0000	0.0000
1000000	15000	15000	25000	**26000**	20000	2000	5.0	37.3954	0.0000	0.0000	1.0499	3.33E+06	1.70E+06	1.66E+06	1.70E+06	0.0000	0.0000
1000000	15000	15000	25000	**27000**	20000	2000	5.0	37.3954	0.0000	0.0000	1.0499	3.33E+06	1.70E+06	1.66E+06	1.70E+06	0.0000	0.0000
1000000	15000	15000	25000	20000	**16000**	2000	5.0	37.3954	0.0238	0.0000	1.0855	1.09E+06	1.09E+06	1.54E+00	1.09E+06	0.0000	0.0000
1000000	15000	15000	25000	20000	**17000**	2000	5.0	37.3954	0.0791	0.0000	1.1436	4.68E+06	6.70E+05	4.03E+06	5.26E+07	0.0000	0.0000
1000000	15000	15000	25000	20000	**22000**	2000	5.0	37.3954	0.0000	0.0000	1.0499	6.51E+06	3.30E+06	3.30E+06	3.29E+06	0.0000	0.0000
1000000	15000	15000	25000	20000	**25000**	2000	5.0	37.3954	0.3707	0.0000	1.4132	0.00E+00	9.52E-01	4.17E-02	5.60E+06	0.0000	0.0000
1000000	15000	15000	25000	20000	**26000**	2000	5.0	37.3954	0.4046	0.0000	1.4488	1.52E+06	1.52E+06	3.86E+00	1.53E+06	0.0000	0.0000
1000000	15000	15000	25000	20000	20000	**1700**	5.0	37.3954	0.0000	0.0000	1.0499	2.47E+06	2.24E-01	2.39E+06	8.66E+06	0.0000	0.0000
1000000	15000	15000	25000	20000	20000	**1800**	5.0	37.3954	0.1857	0.0000	1.2356	8.35E+05	4.23E+05	4.23E+05	4.23E+05	0.0000	0.0000
1000000	15000	15000	25000	20000	20000	**2100**	5.0	37.3954	0.2184	0.0000	1.2356	1.39E+06	7.07E+05	7.07E+05	7.07E+05	0.0000	0.0000
1000000	15000	15000	25000	20000	20000	**2200**	5.0	37.3954	0.0000	0.0000	1.0499	4.16E+06	2.14E+06	2.14E+06	2.13E+06	0.0000	0.0000

N_0	M_0	$\mathbf{L_n}$	$\mathbf{U_n}$	$\mathbf{U_m}$	$\mathbf{U_{vn}}$	$\mathbf{L_{nm}}$	t	$\mathbf{R_{E1}}^*$	β_{11}	β_{21}	δ_{11}	τ_{11}	δ_{21}	τ_{21}	β_{32}	δ_{32}	τ_{32}
1000000	15000	15000	25000	20000	20000	**2400**	5.0	37.3954	0.0000	0.0000	1.0499	5.43E+06	6.66E+04	5.37E+06	1.40E+06	0.0000	0.0000
1000000	15000	15000	25000	20000	20000	2000	**3.0**	49.2802	0.0274	0.0000	1.7772	1.09E+06	1.09E+06	3.48E-01	1.10E+06	0.0000	0.0000
1000000	15000	15000	25000	20000	20000	2000	**3.4**	46.9359	0.2730	0.0000	1.8170	4.95E+05	8.42E-01	4.95E+05	1.96E+06	0.0000	0.0000
1000000	15000	15000	25000	20000	20000	2000	**5.4**	34.9449	0.0000	0.0000	0.9722	3.46E+06	3.43E+06	8.91E-02	3.51E+06	0.0000	0.0000
1000000	15000	15000	25000	20000	20000	2000	**5.6**	33.7047	0.0000	0.0000	0.9374	3.23E+06	3.23E+06	9.70E-02	8.14E+05	0.0000	0.0000
1000000	15000	15000	25000	20000	20000	2000	**6.4**	28.604	0.1706	0.0000	0.9666	1.30E+06	1.30E+06	1.05E-02	1.30E+06	0.0000	0.0000

Appendix-3(b)

Table : Values of R_{E1}*, β_{11}, τ_{11}, δ_{11}, β_{21},δ_{21}, τ_{21}, β_{32}, δ_{32}, τ_{32} for Varying values of one value of the following N_0, M_0, L_n, U_n, U_m,U_{vn}, L_{vm}, t when other parameters are constants (Vacation Period)

N_0	M_0	L_n	U_n	U_m	U_{vn}	L_{nm}	T	R_{E1}*	β_{11}	β_{21}	δ_{11}	τ_{11}	δ_{21}	τ_{21}	β_{32}	δ_{32}	τ_{32}
700000	25000	25000	200000	40000	40000	4000	2.0	36.9840	0.3483	0.0000	2.2698	9.98E+05	9.98E+05	1.36E-01	2.54E+05	0.0000	0.0000
750000	25000	25000	200000	40000	40000	4000	2.0	39.9791	0.0616	0.0000	2.0176	1.05E+06	5.23E+05	5.23E+05	5.23E+05	0.0000	0.0000
800000	25000	25000	200000	40000	40000	4000	2.0	42.9853	0.3567	0.0000	2.3450	8.33E+05	2.43E-01	8.33E+05	8.33E+05	0.0000	0.0000
850000	25000	25000	200000	40000	40000	4000	2.0	46.0015	0.3606	0.0000	2.3792	8.24E+05	8.24E+05	1.79E-01	8.24E+05	0.0000	0.0000
900000	25000	25000	200000	40000	40000	4000	2.0	49.0269	0.3643	0.0000	2.4115	1.18E+06	1.18E+06	3.09E-01	1.18E+06	0.0000	0.0000
1000000	**5000**	25000	200000	40000	40000	4000	2.0	165.3008	0.3713	0.0000	2.4712	4.52E+04	2.26E+04	2.26E+04	2.26E+04	0.0000	0.0000
1000000	**6000**	25000	200000	40000	40000	4000	2.0	137.7554	0.3713	0.0000	2.4712	3.40E+06	6.29E-01	3.40E+06	3.41E+06	0.0000	0.0000
1000000	**9000**	25000	200000	40000	40000	4000	2.0	91.8370	0.0575	0.0000	2.1574	2.64E+06	1.32E+06	1.32E+06	1.32E+06	0.0000	0.0000
1000000	**10000**	25000	200000	40000	40000	4000	2.0	82.6533	0.0546	0.0000	2.1545	2.45E+06	1.23E+06	1.23E+06	1.22E+06	0.0000	0.0000
1000000	**11000**	25000	200000	40000	40000	4000	2.0	75.1393	0.0575	0.0000	2.1574	2.50E+06	1.25E+06	1.25E+06	1.25E+06	0.0000	0.0000
1000000	25000	**8000**	200000	40000	40000	4000	2.0	58.2275	1.8350	0.0000	4.2491	0.00E+00	2.34E+00	6.19E-03	2.72E+07	0.0000	0.0000
1000000	25000	**9000**	200000	40000	40000	4000	2.0	57.7146	1.4631	0.0000	3.8184	6.45E+05	6.45E+05	1.19E-01	2.74E+07	0.0000	0.0000
1000000	25000	**10000**	200000	40000	40000	4000	2.0	57.2294	1.1746	0.0000	3.4771	4.22E+04	4.80E+03	3.74E+04	2.82E+07	0.0000	0.0000
1000000	25000	**11000**	200000	40000	40000	4000	2.0	56.7678	0.9453	0.0000	3.2002	0.00E+00	2.17E+00	6.19E-03	6.36E+07	0.0000	0.0000
1000000	25000	**12000**	200000	40000	40000	4000	2.0	56.3265	0.7595	0.0000	2.9710	9.18E+04	7.06E+03	8.47E+04	2.51E+07	0.0000	0.0000
1000000	25000	**13000**	200000	40000	40000	4000	2.0	55.9031	0.0000	0.0000	2.1714	5.57E+05	5.57E+05	1.19E-01	2.26E+07	0.0000	0.0000
1000000	25000	25000	**25000**	40000	40000	4000	2.0	11.4382	0.0231	0.0000	0.7163	0.00E+00	3.95E-01	5.68E-01	0.0000	73075	73071.9
1000000	25000	25000	**26000**	40000	40000	4000	2.0	11.5345	0.0133	0.0000	0.6868	0.00E+00	3.78E-01	5.70E-01	0.0000	73196.3	73195.2
1000000	25000	25000	**26500**	40000	40000	4000	2.0	11.5820	0.0089	0.0000	0.6729	0.00E+00	3.56E-01	5.84E-01	0.0000	65206.9	65207.9
1000000	25000	25000	**27000**	40000	40000	4000	2.0	11.6291	0.0048	0.0000	0.6595	0.00E+00	3.52E-01	5.81E-01	0.0000	71801.8	71801.2
1000000	25000	25000	**27500**	40000	40000	4000	2.0	11.6757	0.0010	0.0000	0.6465	0.00E+00	3.52E-01	5.74E-01	0.0000	71519.7	71519.1
1000000	25000	25000	200000	**15000**	40000	4000	2.0	55.1022	0.3713	0.0000	2.4712	3.49E+06	1.74E+06	1.74E+06	1.74E+06	0.0000	0.0000
1000000	25000	25000	200000	**14300**	40000	4000	2.0	55.1022	0.3713	0.0000	2.4712	1.26E+06	6.50E+05	6.11E+05	6.10E+05	0.0000	0.0000
1000000	25000	25000	200000	**14900**	40000	4000	2.0	55.1022	0.3713	0.0000	2.4712	1.07E+06	1.07E+06	2.20E-01	1.07E+06	0.0000	0.0000
1000000	25000	25000	200000	**15100**	40000	4000	2.0	55.1022	0.3713	0.0000	2.4712	6.13E+06	3.31E-03	6.13E+06	6.15E+06	0.0000	0.0000
1000000	25000	25000	200000	40000	**27000**	4000	2.0	55.1022	0.0616	0.0000	2.1614	1.28E+06	6.40E+05	6.39E+05	6.40E+05	0.0000	0.0000
1000000	25000	25000	200000	40000	**28000**	4000	2.0	55.1022	0.9398	0.0000	3.0396	8.84E+05	4.42E+05	4.42E+05	4.42E+05	0.0000	0.0000
1000000	25000	25000	200000	40000	**29000**	4000	2.0	55.1022	1.0108	0.0000	3.1107	8.84E+05	4.42E+05	4.42E+05	4.42E+05	0.0000	0.0000
1000000	25000	25000	200000	40000	**30000**	4000	2.0	55.1022	0.1427	0.0000	2.2426	5.92E+04	2.96E+04	2.96E+04	1.69E+06	0.0000	0.0000
1000000	25000	25000	200000	40000	**31000**	4000	2.0	55.1022	1.1530	0.0000	3.2528	1.30E+06	1.30E+06	3.62E-01	1.30E+06	0.0000	0.0000
1000000	25000	25000	200000	40000	40000	**2200**	2.0	55.1022	0.3713	0.0000	2.4712	6.52E+06	6.52E+06	1.19E-01	6.32E+06	0.0000	0.0000
1000000	25000	25000	200000	40000	40000	**2300**	2.0	55.1022	0.0000	0.0000	2.0999	2.87E+04	2.87E+04	1.19E-01	1.11E+07	0.0000	0.0000
1000000	25000	25000	200000	40000	40000	**2400**	2.0	55.1022	0.0000	0.0000	2.0999	1.15E+06	1.15E+06	1.23E-01	1.16E+06	0.0000	0.0000
1000000	25000	25000	200000	40000	40000	**2500**	2.0	55.1022	0.3713	0.0000	2.4712	1.03E+06	1.03E+06	1.23E-01	1.02E+06	0.0000	0.0000
1000000	25000	25000	200000	40000	40000	**2800**	2.0	55.1022	0.3713	0.0000	2.4712	2.81E+07	2.81E+07	1.19E-01	7.45E+06	0.0000	0.0000

N_0	M_0	$\mathbf{L_n}$	$\mathbf{U_n}$	$\mathbf{U_m}$	$\mathbf{U_{vn}}$	$\mathbf{L_{nm}}$	T	R_{E1}*	β_{11}	β_{21}	δ_{11}	τ_{11}	δ_{21}	τ_{21}	β_{32}	δ_{32}	τ_{32}
1000000	25000	25000	200000	40000	40000	4000	**2.3**	53.3602	0.3229	0.0000	2.1488	1.07E+06	2.13E-01	1.07E+06	1.07E+06	0.0000	0.0000
1000000	25000	25000	200000	40000	40000	4000	**2.5**	52.1969	0.2970	0.0000	1.9769	1.24E+06	6.19E+05	6.19E+05	6.19E+05	0.0000	0.0000
1000000	25000	25000	200000	40000	40000	4000	**2.8**	50.4484	0.0652	0.0000	1.5651	7.69E+05	6.11E+05	1.58E+05	6.11E+05	0.0000	0.0000
1000000	25000	25000	200000	40000	40000	4000	**3.0**	49.2802	0.0723	0.0000	1.4722	8.43E+05	4.22E+05	4.22E+05	4.22E+05	0.0000	0.0000
1000000	25000	25000	200000	40000	40000	4000	**3.8**	44.5790	0.0778	0.0000	1.1830	1.17E+06	5.83E+05	5.83E+05	5.83E+05	0.0000	0.0000

Appendix-3(c)

Table : Values of R_{E2}*, β_{11}, τ_{11}, δ_{11}, β_{21},δ_{21}, τ_{21}, β_{32}, δ_{32}, τ_{32} for Varying values of one value of the following N_0, M_0, L_n, U_n, U_m,U_{vn}, L_{vm}, t when other parameters are constants (Drug Administration Period)

N_0	M_0	L_n	U_n	U_m	U_{vn}	L_{nm}	t	R_{E2}*	β_{11}	β_{21}	δ_{11}	τ_{11}	δ_{21}	τ_{21}	β_{32}	δ_{32}	τ_{32}
400000	10000	15000	100000	20000	20000	2000	3.0	1.14E-12	0.2108	0.2493	1.0560	1.3344	1.3372	1.0916	1.3845	1.4105	1.4352
500000	10000	15000	100000	20000	20000	2000	3.0	5.67E-13	0.2189	0.3890	0.9987	1.3075	1.3358	1.1405	1.4852	1.3099	1.3346
800000	10000	15000	100000	20000	20000	2000	3.0	2.61E-13	0.0847	0.3653	0.9833	2.1476	1.3358	2.0758	1.6461	1.1490	1.1247
900000	10000	15000	100000	20000	20000	2000	3.0	1.59E-12	0.2100	0.4198	1.1433	1.3118	1.3358	1.3292	1.3855	1.4095	1.4342
1000000	10000	15000	100000	20000	20000	2000	3.0	1.80E-12	0.1999	0.4129	1.1703	1.3030	1.3358	1.3505	1.3856	1.4094	1.4341
1000000	**11000**	15000	100000	20000	20000	2000	3.0	1.83E-12	0.1997	0.4125	1.1705	1.3030	1.3358	1.3504	1.3856	1.4094	1.4341
1000000	**12000**	15000	100000	20000	20000	2000	3.0	1.84E-12	0.1995	0.4120	1.1707	1.3030	1.3358	1.3504	1.3856	1.4094	1.4341
1000000	**13000**	15000	100000	20000	20000	2000	3.0	1.85E-12	0.1994	0.4116	1.1709	1.3030	1.3358	1.3503	1.3856	1.4094	1.4341
1000000	**14000**	15000	100000	20000	20000	2000	3.0	1.88E-12	0.1992	0.4112	1.1711	1.3030	1.3358	1.3503	1.3856	1.4094	1.4341
1000000	**16000**	15000	100000	20000	20000	2000	3.0	1.89E-12	0.2115	0.4218	1.1772	1.3026	1.3358	1.3543	1.3852	1.4098	1.4345
1000000	10000	**10000**	100000	20000	20000	2000	3.0	2.03E-12	0.2577	0.4705	1.2240	1.2925	1.3523	1.3770	1.3899	1.4051	1.4298
1000000	10000	**13000**	100000	20000	20000	2000	3.0	2.03E-12	0.2468	0.4863	1.1965	1.3030	1.3358	1.4033	1.3856	1.4094	1.4341
1000000	10000	**16000**	100000	20000	20000	2000	3.0	1.85E-12	0.1626	0.3967	1.1363	1.3029	1.3358	1.3375	1.3855	1.4095	1.4342
1000000	10000	**17000**	100000	20000	20000	2000	3.0	1.66E-12	0.1161	0.3808	1.0904	1.3026	1.3358	1.3219	1.3852	1.4099	1.4345
1000000	10000	**18000**	100000	20000	20000	2000	3.0	1.49E-12	0.0526	0.3485	1.0350	1.3027	1.3358	1.2978	1.3852	1.4098	1.4344
1000000	10000	10000	**13000**	20000	20000	2000	3.0	4.11E-12	0.2450	0.4633	1.2293	1.2933	1.3581	1.3828	1.3891	1.4059	1.4306
1000000	10000	10000	**14000**	20000	20000	2000	3.0	2.00E-12	0.2557	0.4507	1.2282	1.2997	1.3498	1.3731	1.3874	1.4076	1.4323
1000000	10000	10000	**15000**	20000	20000	2000	3.0	1.86E-12	0.2659	0.4493	1.2226	1.3093	1.3421	1.3731	1.3893	1.4058	1.4305
1000000	10000	10000	**16000**	20000	20000	2000	3.0	1.89E-12	0.2647	0.4488	1.2215	1.3093	1.3421	1.3727	1.3893	1.4058	1.4305
1000000	10000	10000	**19000**	20000	20000	2000	3.0	3.57E-12	0.2647	0.4488	1.2215	1.3093	1.3421	1.3727	1.3893	1.4058	1.4305
1000000	10000	10000	100000	**5000**	20000	2000	3.0	1.55E-14	0.1960	0.1633	1.5677	2.2649	2.6124	1.1875	517.8064	0.8554	0.9828
1000000	10000	10000	100000	**6000**	20000	2000	3.0	1.65E-13	0.0045	0.1967	1.3429	0.8051	1.1764	1.1637	27.8915	1.0971	0.2705
1000000	10000	10000	100000	**8000**	20000	2000	3.0	1.08E-12	0.0135	0.1262	1.1914	1.3551	0.7743	1.8848	2.2967	0.7124	1.0352
1000000	10000	10000	100000	**9000**	20000	2000	3.0	1.08E-12	0.0312	0.2748	1.2914	0.8163	1.0020	1.3494	1.4769	0.2786	0.2835
1000000	10000	10000	100000	**10000**	20000	2000	3.0	2.08E-13	0.0198	0.3178	1.2271	4.2613	4.4370	1.3494	4.3662	0.1086	0.1135
1000000	10000	10000	100000	**14000**	20000	2000	3.0	7.17E-13	0.2371	0.4633	1.3088	0.8001	1.0171	1.3180	1.3906	0.2836	0.2886
1000000	10000	10000	100000	20000	**15000**	2000	3.0	1.98E-12	0.2241	0.5016	1.2066	1.2865	1.3729	1.3976	1.4060	1.3890	1.4137
1000000	10000	10000	100000	20000	**16000**	2000	3.0	2.07E-12	0.2313	0.4894	1.2077	1.2844	1.3627	1.3874	1.3939	1.4012	1.4259
1000000	10000	10000	100000	20000	**17000**	2000	3.0	2.05E-12	0.2363	0.4665	1.2178	1.2933	1.3583	1.3830	1.3894	1.4056	1.4303
1000000	10000	10000	100000	20000	**18000**	2000	3.0	2.07E-12	0.2473	0.4556	1.2251	1.2965	1.3526	1.3773	1.3869	1.4081	1.4328
1000000	10000	10000	100000	20000	**19000**	2000	3.0	1.97E-12	0.2574	0.4496	1.2273	1.3023	1.3490	1.3728	1.3877	1.4074	1.4320
1000000	10000	10000	100000	20000	20000	**18000**	3.0	4.17E-12	0.4688	0.5551	1.3897	1.2802	1.3935	1.3227	1.3762	1.4189	1.6483
1000000	10000	10000	100000	20000	20000	**20000**	3.0	3.81E-12	0.4071	0.6104	1.3317	1.0980	1.2920	1.3411	1.3814	1.4137	1.4383
1000000	10000	10000	100000	20000	20000	**21000**	3.0	2.25E-13	0.1564	0.4881	1.2034	4.4802	1.5643	4.4509	2.3499	0.4596	0.4701
1000000	10000	10000	100000	20000	20000	**22000**	3.0	2.24E-13	0.1553	0.4870	1.2033	4.5536	1.5643	4.5243	2.3400	0.4694	0.4800

N_0	M_0	$\mathbf{L_n}$	$\mathbf{U_n}$	$\mathbf{U_m}$	$\mathbf{U_{vn}}$	$\mathbf{L_{nm}}$	**t**	$\mathbf{R_{E2}}^*$	β_{11}	β_{21}	δ_{11}	τ_{11}	δ_{21}	τ_{21}	β_{32}	δ_{32}	τ_{32}
1000000	10000	10000	100000	20000	20000	**23000**	3.0	2.26E-14	0.3547	0.6115	1.2782	63.4283	1.8054	63.1579	1.5786	1.2164	1.2411
1000000	10000	10000	100000	20000	20000	2000	**2.5**	2.18E-13	0.2000	0.5917	1.4503	4.5465	1.5645	4.8240	4.6329	0.8940	0.8978
1000000	10000	10000	100000	20000	20000	2000	**3.4**	2.23E-13	0.1980	0.2527	1.1734	1.6698	1.3116	1.5864	5.4597	0.8551	0.8798
1000000	10000	10000	100000	20000	20000	2000	**3.8**	1.53E-13	0.0945	0.0109	1.1514	0.8654	0.6326	0.2327	0.3241	1.6480	1.6529
1000000	10000	10000	100000	20000	20000	2000	**4.0**	2.26E-23	0.0379	0.0984	0.9312	2.2591	1.0861	2.1647	0.3449	0.8422	1.0230
1000000	10000	10000	100000	20000	20000	2000	**4.8**	9.80E-24	0.0482	0.2260	0.6561	3.3709	1.4835	2.7213	0.3501	0.2129	0.8665

Appendix-3(d)

Table : Values of R_{E2}*, β_{11}, τ_{11}, δ_{11}, β_{21},δ_{21}, τ_{21}, β_{32}, δ_{32}, τ_{32} for Varying values of one value of the following N_0, M_0,L_n, U_n, U_m,U_{vn}, L_{vm}, t when other parameters are constants (Drug vacation period)

N_0	M_0	L_n	U_n	U_m	U_{vn}	L_{nm}	T	R_{E2}*	β_{11}	β_{21}	δ_{11}	τ_{11}	δ_{21}	τ_{21}	β_{32}	δ_{32}	τ_{32}
100000	20000	25000	200000	40000	40000	4000	3.0	1.28E-13	0.10975	0.28007	0.46059	1.37058	1.00075	1.00075	1.00074	0.99926	0.99926
300000	20000	25000	200000	40000	40000	4000	3.0	8.04E-24	0.15077	0.37113	0.75378	1.72874	1.33910	1.36378	1.40164	1.42221	1.76575
400000	20000	25000	200000	40000	40000	4000	3.0	8.32E-14	0.18622	0.42415	0.84744	1.36755	1.36248	1.09045	4.04545	1.39667	1.42136
600000	20000	25000	200000	40000	40000	4000	3.0	2.84E-13	0.00000	0.31627	0.80575	1.84173	1.37454	1.58921	1.42562	1.38177	1.40646
900000	20000	25000	200000	40000	40000	4000	3.0	2.92E-13	0.00000	0.32464	0.93922	1.58933	1.41425	1.43894	1.47423	1.37335	0.41677
1000000	**11000**	25000	200000	40000	40000	4000	3.0	2.41E-12	0.18621	0.29323	1.27133	1.32902	1.34135	1.36602	1.39192	1.41547	1.44016
1000000	**12000**	25000	200000	40000	40000	4000	3.0	2.42E-12	0.18620	0.29324	1.27132	1.32902	1.34135	1.36602	1.39192	1.41547	1.44016
1000000	**14000**	25000	200000	40000	40000	4000	3.0	2.44E-12	0.18620	0.29325	1.27131	1.32902	1.34135	1.36602	1.39192	1.41546	1.44015
1000000	**16000**	25000	200000	40000	40000	4000	3.0	2.47E-12	0.18620	0.29326	1.27129	1.32902	1.34135	1.36602	1.39193	1.41546	1.44015
1000000	**18000**	25000	200000	40000	40000	4000	3.0	2.50E-12	0.18620	0.29327	1.27128	1.32902	1.34135	1.36602	1.39193	1.41546	1.44015
1000000	**24000**	25000	200000	40000	40000	4000	3.0	2.57E-12	0.18621	0.29330	1.27127	1.32892	1.34130	1.36598	1.39193	1.41561	1.44015
1000000	20000	**16000**	200000	40000	40000	4000	3.0	2.28E-12	0.16648	0.29272	1.24474	1.33132	1.33881	1.36349	1.39169	1.41570	1.44039
1000000	20000	**17000**	200000	40000	40000	4000	3.0	2.06E-12	0.12830	0.29212	1.19221	1.33610	1.33372	1.35840	1.39138	1.41601	1.44070
1000000	20000	**18000**	200000	40000	40000	4000	3.0	5.45E-11	0.06943	0.35799	1.04233	1.34780	1.33023	1.34845	1.39135	1.41604	1.57612
1000000	20000	**19000**	200000	40000	40000	4000	3.0	1.66E-12	0.03701	0.34195	1.01081	1.35007	1.33260	1.33322	1.39131	1.41608	1.55700
1000000	20000	**20000**	200000	40000	40000	4000	3.0	1.42E-12	0.00000	0.29233	1.01168	1.33990	1.33074	1.31317	1.39135	1.41604	1.44073
1000000	20000	25000	**15500**	40000	40000	4000	3.0	2.58E-13	0.21573	0.42677	1.17793	1.74898	1.55663	1.58132	3.78418	1.21249	1.23718
1000000	20000	25000	**15750**	40000	40000	4000	3.0	6.17E-13	0.20080	0.41998	1.16449	1.74886	1.55392	1.57861	3.73562	1.22033	1.24502
1000000	20000	25000	**16500**	40000	40000	4000	3.0	5.93E-14	0.14346	0.42148	1.10686	12.47859	1.74432	12.11915	4.24540	1.07232	1.08528
1000000	20000	25000	**17000**	40000	40000	4000	3.0	1.70E-09	0.00000	0.01421	1.38569	1.89847	0.13200	1.76647	0.46211	1.44938	1.46790
1000000	20000	25000	**17500**	40000	40000	4000	3.0	1.92E-13	0.00000	0.01402	1.36542	3.76969	1.87250	1.89719	5.20203	0.82074	0.84543
1000000	20000	25000	**90000**	40000	40000	4000	3.0	2.40E-12	0.18621	0.29323	1.27133	1.32902	1.34135	1.36602	1.39192	1.41547	1.44016
1000000	20000	25000	200000	**10000**	40000	4000	3.0	5.63E-13	0.09929	0.15560	1.28767	2.74342	2.28740	1.80000	1.82921	0.59846	1.05999
1000000	20000	25000	200000	**12000**	40000	4000	3.0	2.57E-13	0.21278	0.25380	1.34690	6.09295	1.33075	6.15012	1.60417	0.91273	0.92013
1000000	20000	25000	200000	**13000**	40000	4000	3.0	3.96E-11	0.00261	0.00398	1.29714	0.68243	0.41975	0.26268	0.51561	2.29179	1.32201
1000000	20000	25000	200000	**15000**	40000	4000	3.0	2.36E-12	0.18363	0.30824	1.25279	1.30879	1.33076	1.35543	1.39135	1.41604	1.44073
1000000	20000	25000	200000	**16000**	40000	4000	3.0	2.46E-12	0.19053	0.29206	1.27841	1.32426	1.33825	1.36594	1.39135	1.41604	1.44073
1000000	20000	25000	200000	**17000**	40000	4000	3.0	3.49E-12	0.18621	0.29317	1.27139	1.32902	1.34135	1.36602	1.39192	1.41547	1.44016
1000000	20000	25000	200000	40000	**16000**	4000	3.0	4.58E-12	0.00000	0.38110	0.99182	1.51032	1.42928	1.45397	0.65592	1.32923	1.35392
1000000	20000	25000	200000	40000	**18500**	4000	3.0	2.35E-12	0.14267	0.29416	1.23636	1.32619	1.34468	1.36936	1.39243	1.41496	1.43965
1000000	20000	25000	200000	40000	**19000**	4000	3.0	2.48E-12	0.18145	0.29662	1.27796	1.32528	1.34686	1.37154	1.39369	1.41370	1.43839
1000000	20000	25000	200000	40000	**19500**	4000	3.0	2.47E-12	0.18502	0.29368	1.27741	1.32662	1.34401	1.36868	1.39218	1.41521	1.43990
1000000	20000	25000	200000	40000	**20000**	4000	3.0	2.40E-12	0.18621	0.29323	1.27133	1.32902	1.34135	1.36602	1.39192	1.41547	1.44016
1000000	20000	25000	200000	40000	**21000**	4000	3.0	2.36E-12	0.18853	0.29232	1.25971	1.33366	1.33624	1.36092	1.39147	1.41592	1.44061
1000000	20000	25000	200000	40000	40000	**11500**	3.0	2.40E-12	0.18621	0.29323	1.27133	1.32902	1.34135	1.36602	1.39192	1.41547	1.44016

N_0	M_0	$\mathbf{L_n}$	$\mathbf{U_n}$	$\mathbf{U_m}$	$\mathbf{U_{vn}}$	$\mathbf{L_{nm}}$	T	R_{E2}*	β_{11}	β_{21}	δ_{11}	τ_{11}	δ_{21}	τ_{21}	β_{32}	δ_{32}	τ_{32}
1000000	20000	25000	200000	40000	40000	**12500**	3.0	3.02E-13	0.00000	0.44110	0.95879	1.49336	1.36359	1.52967	2.87962	1.22993	1.25462
1000000	20000	25000	200000	40000	40000	**13000**	3.0	2.03E-13	0.04722	0.39220	1.01606	1.99353	1.36359	1.99098	2.12748	0.67991	0.31540
1000000	20000	25000	200000	40000	40000	**14000**	3.0	3.13E-13	0.16449	0.44111	1.12328	1.81143	1.36359	1.84774	1.92475	0.88264	0.35843
1000000	20000	25000	200000	40000	40000	**14500**	3.0	9.26E-14	0.20982	0.41474	1.18196	8.49868	4.30962	5.57595	5.59806	2.01671	2.06609
1000000	20000	25000	200000	40000	40000	4000	**2.0**	2.45E-13	0.00000	0.66167	1.43819	1.18336	2.00524	1.27797	4.04410	0.47539	0.48280
1000000	20000	25000	200000	40000	40000	4000	**2.4**	2.44E-13	0.08033	0.53637	1.29383	3.68143	3.90038	1.53093	1.97249	0.91645	1.03945
1000000	20000	25000	200000	40000	40000	4000	**3.2**	2.51E-12	0.21550	0.28858	1.23933	1.35103	1.31938	1.34406	1.39197	1.41542	1.44011
1000000	20000	25000	200000	40000	40000	4000	**4.0**	3.67E-23	0.01978	0.25226	0.75045	1.84748	1.36798	1.46242	1.42788	1.37950	1.67864
1000000	20000	25000	200000	40000	40000	4000	**4.2**	2.14E-13	0.00000	0.31508	0.68485	3.06915	1.35357	2.71551	1.44206	1.36533	1.11618